



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 51

Alan R. Katritzky

Advances in

# Heterocyclic Chemistry

Volume 51

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Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

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## Preface

Volume 51 of *Advances* consists of three chapters, V. V. Mezheritskii and V. V. Tkachenko (Rostov-on-Don, U.S.S.R.) review the synthesis of peri-annelated heterocycles, a large and interesting class which has not previously been treated in a systematic fashion. R. M. Acheson (Oxford, U.K.) provides the first detailed survey of 1-hydroxypyrroles and their benzo derivatives, compounds which show an interesting and unusual chemistry. Finally, B. A. Trofimov (Irkutsk, U.S.S.R.) describes the mini-fold preparative possibility for pyrroles from ketoximes and acetylenes, a reaction discovered by Trofimov and developed by him into a most important entry into pyrrole chemistry.

Volume 51 should have been an "Index Volume," and indeed the indices were already in an advanced stage, when serious illness in the indexer's immediate family prevented their inclusion in this volume. They will appear in a later volume.

A. R. KATRITZKY



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# Synthesis of Peri-Annulated Heterocyclic Systems

VALERII V. MEZHERITSKII AND VERA V. TKACHENKO

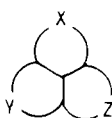
*Research Institute of Physical and Organic Chemistry,  
Rostov-on-Don University, 344006 Rostov-on-Don, U.S.S.R.*

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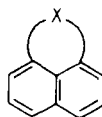
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## I. Introduction

Peri-annelated (peri-condensed) heterocyclic systems imply structures **1** (where X is a heteroatom; Y, Z are heteroatoms or a hydrocarbon fragment), which contain a tricyclic nucleus where the heterocycle is linked to two other rings at the contiguous sides. In this review, we are restricted to the description of monoheterocyclic systems linked to a carbocyclic benzenoid nucleus. The peri-annelated heterocyclic naphthalene derivatives **2** (where X is a heteroatom) are the simplest representatives of this class of compounds.



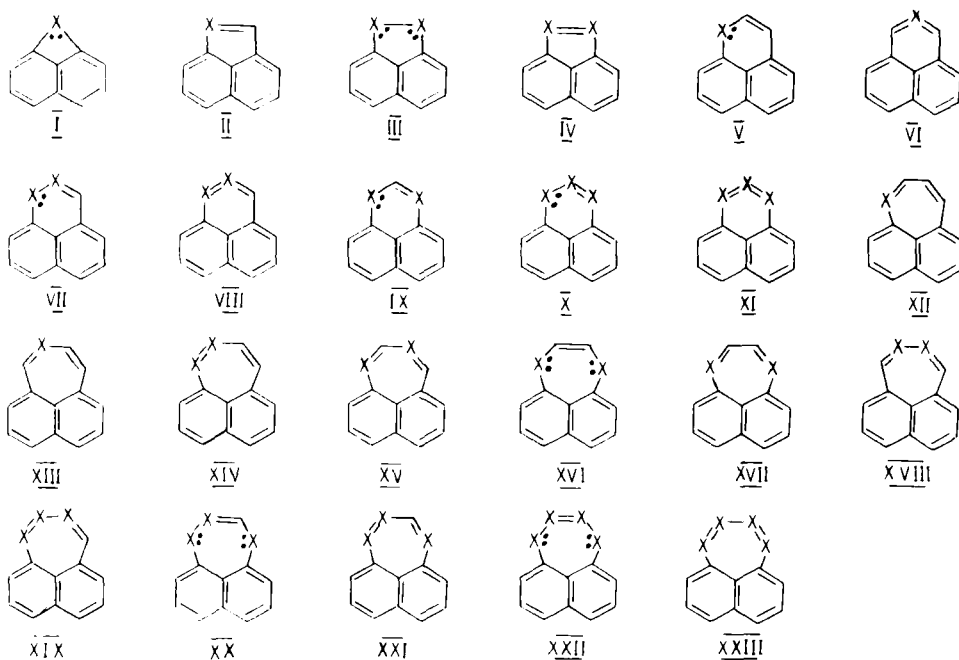
(1)



(2)

where X is heteroatom, Y,Z are heteroatoms or a hydrocarbon fragment

Naphthalene peri-heterocycles with the united closed-loop  $\pi$ -system (**I–XXIII**, where X = O, O<sup>+</sup>, S, S<sup>+</sup>, SO, SO<sub>2</sub>, N, RN, RN<sup>+</sup>, etc., and X may be the same or different heteroatoms) are conveniently classified by the number of members and heteroatoms in a heterocyclic ring. Peri-heterocyclic systems with four to seven-membered heterorings are discussed here. In each particular case, the number of peri-heterocyclic



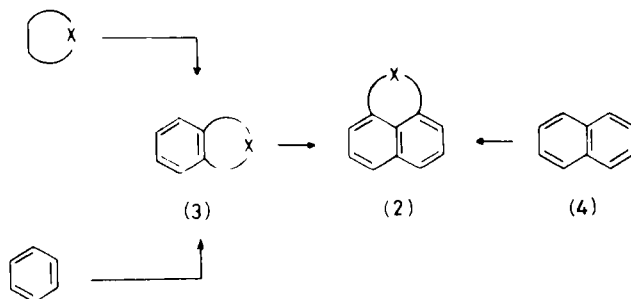
where X is O, O<sup>+</sup>, S, S<sup>+</sup>, SO, SO<sub>2</sub>, N, RN, RN<sup>+</sup>, etc., and X may be the same or the different heteroatoms.

derivatives for structures **I-XXIII** varies depending on the nature and the different valent states of heteroatoms as well as on the nature, position, and number of substituents. Moreover, one should bear in mind such forms do not have an alternation of multiple bonds as in structures **I-XXIII**, but these forms can assume such an alternation as the result of mesomeric or tautomeric change (**1a**, **1b**; **2a**, **2b**).



The subject of this review is a systematization of synthetic methods for constructing a skeleton of a peri-heterocyclic nucleus (with closed-loop and nonclosed-loop<sup>1</sup>  $\pi$ -systems) from precursors that do not contain such a nucleus. Conversions of peri-annelated heterocyclic rings and recycli-

<sup>1</sup> Heterocyclic compounds are implied where a conjugated system is broken by  $sp^3$ -hybridized carbon atoms at least in the case of three-membered peri-linked rings. Such compounds are often predecessors of the closed-loop  $\pi$ -systems I-XXIII.

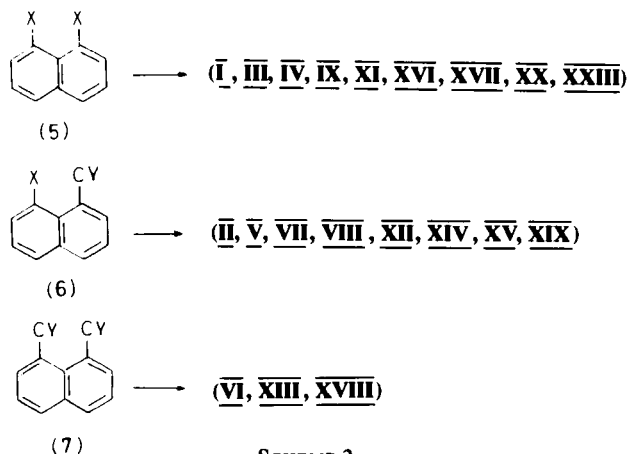


SCHEME 1

zation reactions with heteroatom exchange are also considered in this systematization. Syntheses of peri-heterocycles based on transformations of substituents are conveniently classified under the chemical properties of these systems and discussed in the corresponding sections.

The construction of peri-annulated heterocyclic systems **I–XXIII** is carried out by the addition of a three carbon-atom fragment to the benzoheterocycle (**3** → **2**) or of a heterocycle to a naphthalene nucleus (**4** → **2**) (see Scheme 1). In practice, the second approach (**4** → **2**) is used more often. 1,8-Disubstituted naphthalene derivatives serve as the initial compounds, and they may be divided into three main types (**5–7**) as potential precursors of peri-heterocycles **I–XXIII** (Scheme 2).

The principles of construction of peri-heterocycles in many cases may be applied to syntheses of other peri-systems depicted by the general formula **1**. Besides the naphthalene series **X–XXIII**, syntheses of some of their benzologs are discussed in this review, including the syntheses of



SCHEME 2

anthracene derivatives. Information in the latter case has been taken from the monograph by M. V. Gorelik (83MI1)<sup>2</sup>.

The nomenclature of peri-naphthalene heterocycles does not follow a common principle. In many original papers, the names of heterocyclic systems are derived from the corresponding peri-annelated hydrocarbon derivatives (1,2-diazaacenaphthylene, 1-oxaphenalene, etc.), from mono-heterocycles with an indication of linked positions (naphtho[1,8-*bc*]furan, naphtho[1,8-*de*]azepine, etc.), and from benzoannelated heterocycles (benzo[*cd*]indole, benzo[*de*]quinoline, etc.). Some heterocyclic systems and some compounds have trivial names, for instance, perimidine, naphthostyryl, and naphtholactone. Moreover, it is necessary to remember some peculiarities in the electronic structure of peri-annelated heterocycles, namely the absence of independent existence of the  $\pi$ -closed-loop monoheterocycles which could be a fragment of peri-annelated heterocyclic systems. Therefore, the separation of a heterocycle from the united  $\pi$ -system is impossible. In this case, the simplest structure and the  $\pi$ -electron unit is the whole peri-heterocyclic nucleus.

One should notice also that for pairs of compounds with the same number of members, a "pyrrole-type" heteroatom in monocyclic or in benzoannelated systems corresponds to a "pyridine-type" heteroatom in the peri-heterocyclic ring.

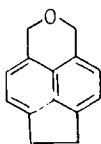


Since the chemical nature of a heterocyclic system is determined by the valent state of the heteroatom, on the basis of data described previously in this review, one could not consider the names used for a lot of peri-heterocycle series to be very suitable. Thus, indole is a  $\pi$ -excess system, and so-called benzo[*cd*]indole **II** ( $X = N$ ) is a  $\pi$ -deficient one whose properties more resemble pyridine and quinoline. But by analogy, there are some common features in the chemical behavior of azepine and naphtho[*bc*]azepine **XII** ( $X = N$ ) (as one example).

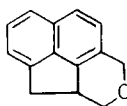
It could be more correct to form peri-heterocyclic nomenclature in accordance with the unified principle based on the names of the corresponding peri-cyclic hydrocarbons; for example, 1-azaacenaphthylene instead of benzo[*cd*]indole and 1-oxaphenalene instead of naphtho[*bc*]pyrane. However, we tried to use as a rule the adopted names. Moreover, for

<sup>2</sup> The authors are greatly thankful to Professor M. V. Gorelik for kind permission to use some data presented in his monograph.

naphthalene derivatives **I–XXIII**, in using the number indexes 1 and 8, which has been accepted in literature, it is unnecessary to resort to new nomenclature, since these positions are the only ones to be linked to the contiguous sides. In those cases when variations of a peri-linkage are possible, it is necessary to use both a number and a letter index, for instance, acenaphtho[4,5-*cd*]pyran **8** and acenaphtho[1,2-*cd*]pyran **9**. As for anthracene derivatives, the trivial names from the monograph (83MI1) are used here.



(8)



(9)

Information about some representatives of peri-heterocyclic naphthalene derivatives has been published in monographs (63MI1; 66MI1; 79HOU414). Advances in the chemistry of perimidine **IX** ( $X = N, NR$ ) have been described in a review (81UK1559), and another review in Japanese (81MI2) has been devoted to periheterocycles **I** with a four-membered heteroring. The structural peculiarities and the original  $\pi$ -system topology result in a specific chemical behavior or peri-annulated heterocycles that makes them extremely interesting objects both for theoretical and experimental investigations. These compounds are a unique source for generating 1,8-dehydronaphthalenes, ylid structures, and other very active intermediates taking part in a series of unusual transformations.

Peri-heterocycles serve as dyes, luminophores, energochromophores, organic conductors, and bioactive compounds. Since the aim of this review is the illustration of major construction principles of the peri-heterocyclic nucleus, the authors do not claim an exhaustive review of all syntheses.

## II. Syntheses of Peri-Annulated Heterocycles

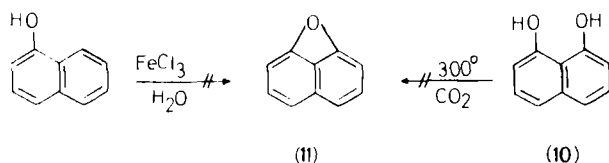
### A. PERI-HETEROCYCLES WITH FOUR-MEMBERED HETERORING

Naphthalene derivatives in which positions 1 and 8 are linked by one heteroatom are the simplest representatives of the peri-annulated heterocyclic systems. Compounds in this group are interesting because of possi-

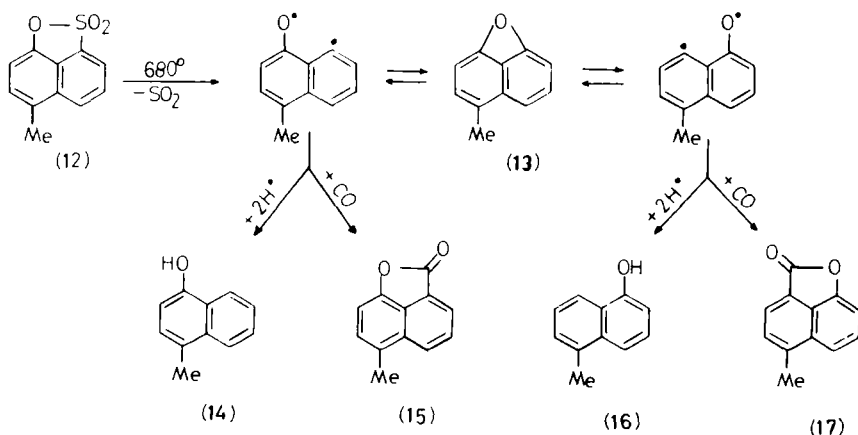
ble distortions of bond lengths and valence angles in the naphthalene nucleus and also in terms of the increased tendency of the four-membered heterocycle towards ring-opening.

### 1. *Naphtho[bc]oxete*

The first information about the synthesis of naphtho[*bc*]-oxete **11** (33BRP394511) was incorrect (70JOC4261). Oxidation of  $\alpha$ -naphthol by ferric chloride or the attempted dehydration of 1,8-dihydroxynaphthalene **10** led to complex mixtures where the desired compound **11** was not detected (70JOC4261).



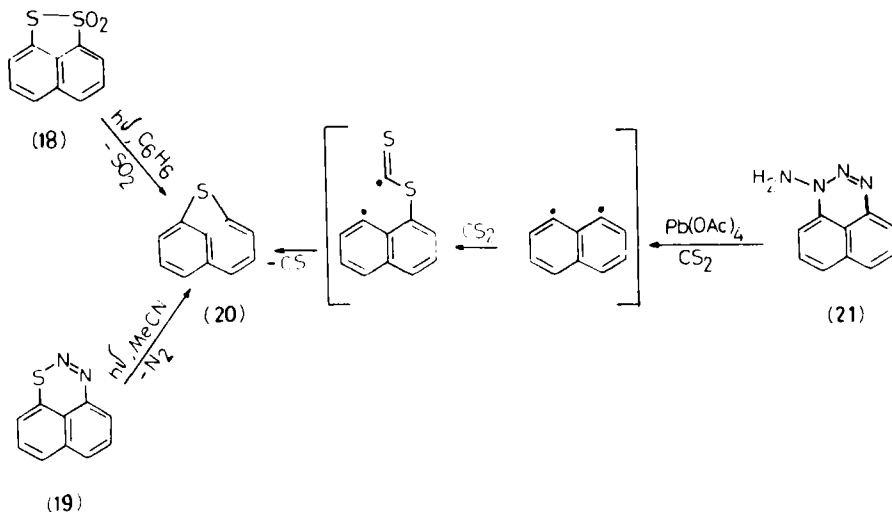
However, arguments proving the existence of naphtho[*bc*]-oxete derivatives have been obtained. Thus, the formation of isomeric pairs of methyl naphthols **14** and **16** and methyl naphtholactones **15** and **17** on pyrolysis of naphtho[*cd*]oxathiol *S,S*-dioxide **12**, having a methyl substituent as a label, in a carbon dioxide or methanol atmosphere is in good agreement with the assumption of the intermediate formation of 4-methylnaphtho[*bc*]oxete **13** (71TL4093). Probably, the attempted isolation of naphtho[*bc*]oxete and its derivatives must exclude severe conditions following their generation because of their high reactivity.



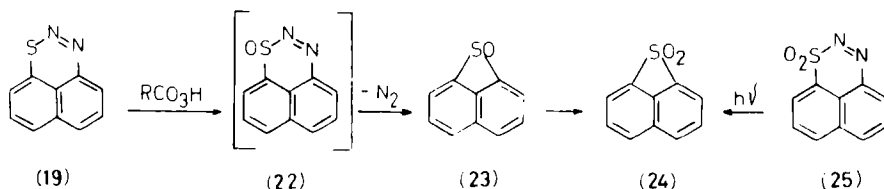


## 2. Naphtho[bc]thiete

Unlike naphtho[bc]oxete, described previously, its thio analog **20** is a stable compound which can be obtained in high yield (97–100%) on photolysis of naphtho[cd]thiol *S,S*-dioxide **18** (76JA6643) or naphtho[de]-thiadiazine **19** (79JA7684). Naphtho[bc]thiete **20** is also formed in low



yield (6–8%) in a mixture with other products on oxidation of 1-aminonaphtho[de]thiadiazine **21** by lead tetraacetate in carbon disulfide [81JCS(P1)413]. The oxidation of naphtho[de]thiadiazine **19** by *m*-chloroperbenzoic acid results in a mixture of naphtho[bc]thiete *S*-oxide **23** and *S,S*-dioxide **24** (79JA7684), instead of the expected naphtho[de]thiadiazine system *S*-oxide **22**.

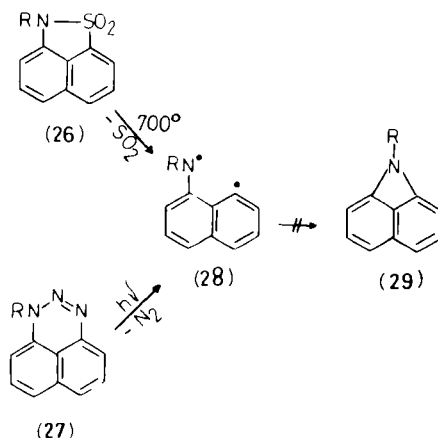


An equimolar ratio of a substrate and oxidizing agent gives oxides **23** and **24** in yields of 71% and 4%, respectively, whereas triple the amount of oxidizing agent leads only to dioxide **24** in 93% yield. The intermediate naphtho[de]thiadiazine *S*-oxide **22** is unstable, and it is decomposed with nitrogen elimination even at room temperature. Dioxide **24** may be obtained only on oxidation of monoxide **23**, and not via the formation of

naphtho[*de*]thiadiazine **25** followed by its decomposition, since it is known that the latter compound is stable at room temperature. Compound **25**, however, can be converted into naphtho[*bc*]thiete *S,S*-dioxide **24** on irradiation [65AG(E)786; 67LA96].

### 3. Naphtho[*bc*]azete

It was impossible to obtain naphtho[*bc*]azete on pyrolysis or on photolysis of *N*-substituted naphtho[*cd*]thiaazole and naphtho[*de*]triazine *S*-oxides **26** and **27**, respectively [69JA1035; 70JCS(C)298]. Unfortunately, formation of the azete intermediates **29** from biradical **28** was not proved even indirectly, as was done, for instance, in the case of formation of the oxygen analogs **13**, i.e., a substituent label was not introduced in the naphthalene nuclei of the initial compounds **26** and **27**.



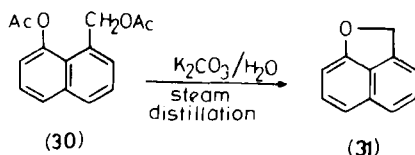
## B. PERI-HETEROCYCLES WITH FIVE-MEMBERED HETERORING AND SINGLE HETEROATOM

Oxygen and sulfur-containing peri-heterocycles (structure **II**) are cations ( $x = O^+, S^+$ ), whereas the nitrogen derivatives **II** may exist as neutral ( $X = N$ ) and cationic ( $X = N^+ - R$ ) forms. Cations of type **II** ( $X = O^+, S^+, N^+ - R$ ) possess a very high reactivity determined not only by the charge but also by the strain in the five-membered heteroring due to the distortion of the normal valence angles at atoms  $C_1$  and  $C_8$  in the naphthalene nucleus. As the result of the strain in the heteroring, the  $X-C_2$  bond is stretched, and it can be easily cleaved in chemical reactions. Thus, the hydrolytic ring-opening in naphtho[*bc*]-

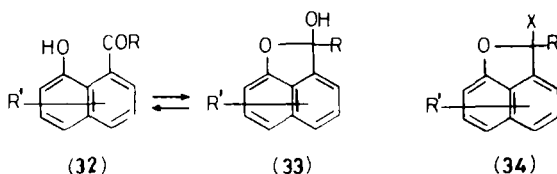
furylium and benzo[*cd*]indolium cations leads to peri-hydroxy and peri-amino-substituted carbonylnaphthalene derivatives, respectively. These compounds play an important role as key initial substances in syntheses of various peri-annulated heterocyclic systems (see Scheme 1).

## 1. Naphtho[*bc*]furans

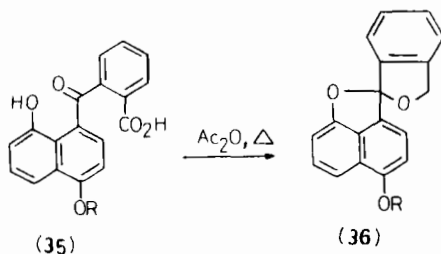
a. *Syntheses from Naphthalene Derivatives.* The most simple pathway to the formation of the naphtho[*bc*]furan nucleus is the heterocyclization of peri-hydroxy-substituted  $\alpha$ -hydroxymethyl or  $\alpha$ -carbonyl naphthalene derivatives. Thus, the simplest 2*H*-naphtho[*bc*]furan **31** is formed



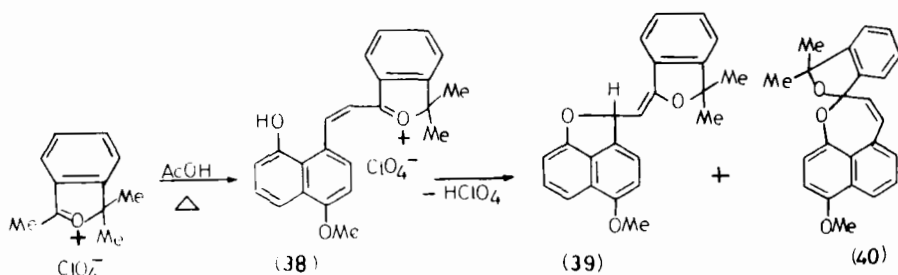
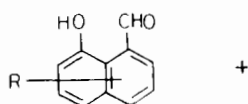
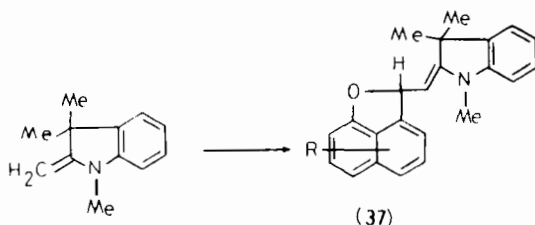
in good yield on treating an aqueous alkaline suspension of 8-acetoxy-1-acetoxymethylnaphthalene **30** with steam [72JCS(P1)699]. Probably, peri-hydroxy-substituted naphthaldehydes and naphthyl ketones **32** exist in solutions in equilibrium with a cyclic form **33** [60CRV555; 67JCS(C)2194; 72JCS(P1)699; 76KPS249; 79ZOR196; 82M11].



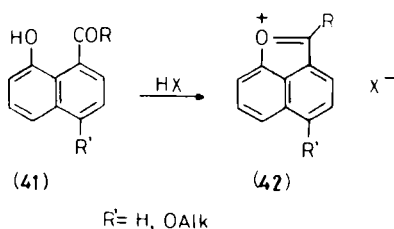
If  $R'$  is a hydrogen atom or an electron-donor group, the equilibrium is accented to the ring-opened isomer **32**, whereas a strong electron-withdrawing substituent accents the equilibrium to another side. Thus, 5,7-dinitro-8-hydroxynaphthaldehyde exists as a cyclic form **33** either in condensed phase or in solutions. The cyclic form **34** ( $X = \text{NHAr}$ ,  $R = \text{H}$ ) is also characteristic of 8-hydroxy-5-nitronaphthaldehyde anils (82M11). The cyclic acetals **34** ( $X = \text{OAlk}$ ) are formed on O-alkylation of peri-hydroxynaphthaldehydes **32** ( $R = \text{H}$ ) (75IJC865; 79BAU1003) or peri-hydroxynaphthyl ketones **32** ( $R = \text{Me, Ph}$ ) [67JCS(C)2194]. Heating ortho-carboxyaryl-peri-hydroxynaphthyl ketones **35** in acetic anhydride leads to a double heterocyclization, resulting in spiro system **36** [71JCS(C)469].



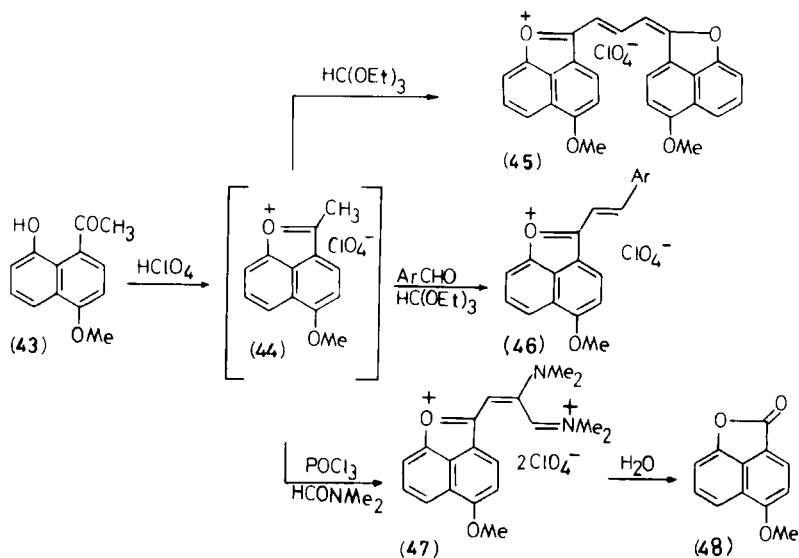
On condensation of peri-hydroxynaphthaldehydes with the Fischer base (82KGS1501) or with 1,3,3-trimethylisobenzofurylium perchlorate (86DOK639), 2-substituted heterocyclic 2*H*-naphtho[*bc*]furan derivatives **37** and **39** have been obtained. Heterocyclization of the condensed product **38** proceeds by the action of bases and results in ring-closed five- and seven-membered heterocycles. Compounds **39** and **40** thus formed have been separated by chromatography.



Peri-hydroxynaphthyl ketones **41** ( $\text{R} = \text{Alk}, \text{Ar}, \text{CH}=\text{CHAr}$ ) and  $\beta$ -diketones **41** ( $\text{R} = \text{CH}_2\text{COAr}$ ) are converted into naphtho[*bc*]furylium salts **42** by the action of strong mineral acids, whereas peri-hydroxynaphthaldehydes do not form the corresponding cations **42** ( $\text{R} = \text{H}$ ) [67JCS(C)2194; 72JCS(P1)699; 77KGS1693; 78ZOR1986; 79ZOR196; 80ZOR1277; 81ZOR1747].

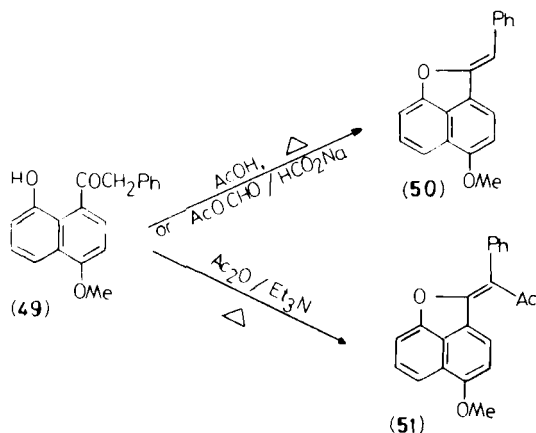


2-Alkyl-naphtho[bc]furylium salts **42** ( $R = \text{Alk}$ ) are easily hydrolyzed even on filtration into their initial ketones **41**, but these salts are stable in sulfuric acid solution. 2-Aryl-, 2-styryl-, and 2-( $\beta$ -hydroxy)styryl-naphtho[bc]furylium perchlorates **42** [ $R = \text{Ar}, \text{CH}=\text{CHAr}, \text{CH}=\text{CH}(\text{OH})\text{Ar}$ ] have been isolated in a crystalline state. On reacting peri-hydroxynaphthylmethyl ketone **43** with ethylorthoformate, aromatic aldehydes, or the Vilsmeier complex under conditions of acidic catalysis, the primary step is closure of the five-membered ring; then, condensations of the 2-methyl group in the newly formed cation **44** result in 2-substituted naphtho[bc]furylium salts **45–47** (78ZOR1986; 79ZOR881). Following reaction of peri-hydroxy ketone **43** with the Vilsmeier complex, 5-methoxynaphtholactone **48** has been isolated as the final product; this lactone is the result of hydrolytic splitting of the cation **47**.

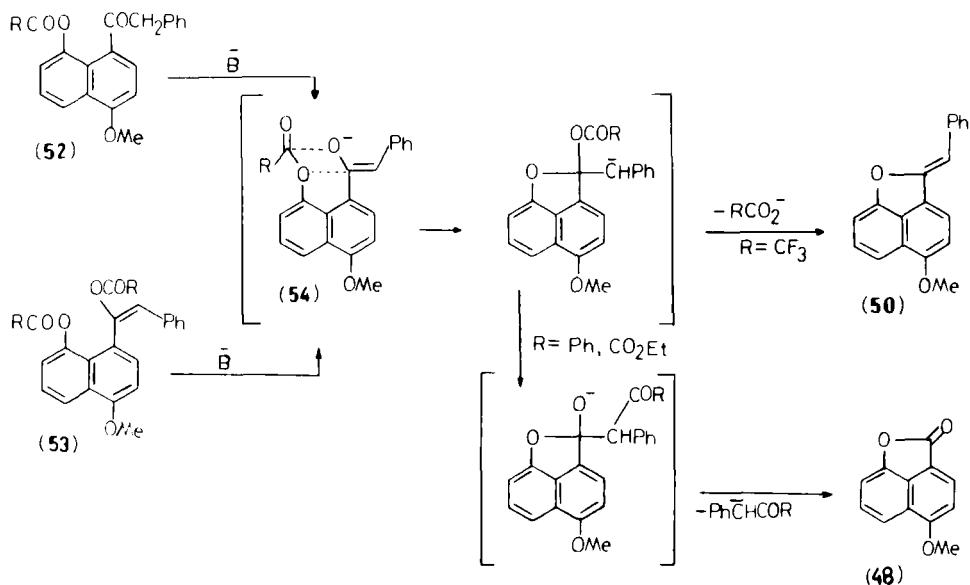


Naphtho[bc]furan derivatives are formed from peri-hydroxynaphthylbenzyl ketone **49** by acidic or basic catalysis (83ZOR411;

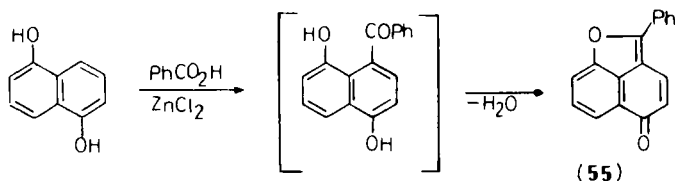
86ZOR2398). Thus, on heating this compound in glacial acetic acid or in formyl acetate in the presence of sodium formate, 2-benzylidene-5-methoxynaphtho[*bc*]furan **50** has been obtained, whereas extended boiling of **49** in a mixture of acetic anhydride and triethylamine has led to *C*-acetyl derivative **51**.



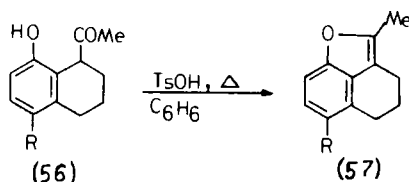
Enolate anions **54**, which can be generated from peri-acyl-oxy-substituted naphthyl benzyl ketones **52** or from their enolacylates **53**, undergo rearrangement into 5-methoxynaphtholactone **48** or 2-benzyl-



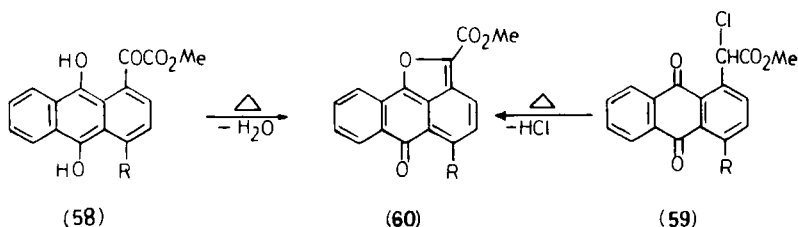
idene-5-methoxynaphtho[*bc*]furan **50**; the result of this rearrangement depends on the nature of the migrating acyl fragment. Fusion of 1,5-dihydroxynaphthalene with benzoic acid and zinc chloride gives rise to 2-phenylnaphtho[*bc*]furan-5-one **55** [71JCS(C)2166].



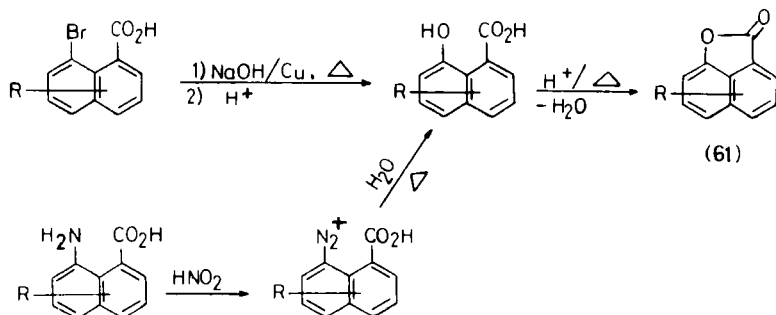
On heating with toluene sulfonic acid in benzene, peri-ace-tylhydroxy-tetralin **56** is converted into 2-methyl-3,4,5-trihydro-naphtho[*bc*]furan **57**



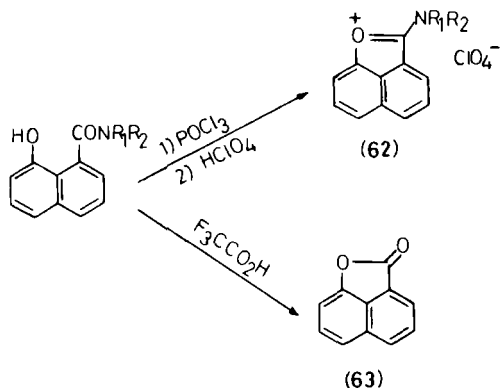
(80TL4391). The benzologs of naphtho[*bc*]furan-6-ones **60** (so-called furan-anthrone) are obtained by cyclization of anthracene peri-hydroxy ketones **58** or carbomethoxychloromethylanthraquinones **59** (80MI3; 84ZOR818).



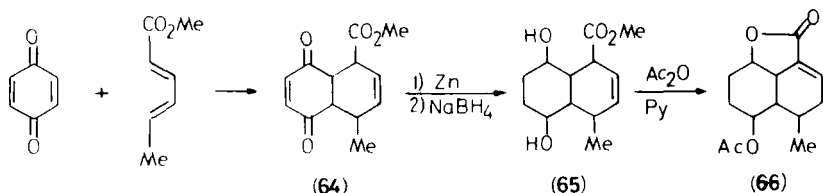
The dehydration of peri-hydroxynaphthoic acids, which can be obtained from peri-bromo- or peri-aminonaphthoic acids, gives rise to naphtho-



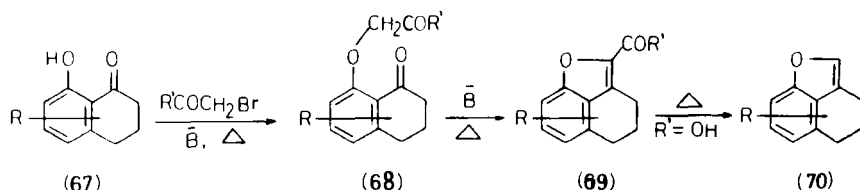
lactones **61** [1886CB1131; 1888JPR241; 32JCS2728; 58ZOB2944; 66JCS(C)523, 66ZOR1063; 67ZOR103; 69ZOR479]. On boiling with excess phosphorus oxychloride, amides of peri-hydroxynaphthoic acid form N-substituted 2-aminonaphtho[*bc*]furylium salts **62**, whereas naphtholactone **63** has been obtained on heating the same amides in trifluoroacetic acid (87ZOR167).



A [4 + 2] cycloaddition is used for constructing bicyclic quinone **64**, which is then reduced to  $\gamma$ -hydroxyme-thylcarboxylate **65**. The latter is cyclized to lactone **66**, which has a skeleton of naphtho[*bc*]furan



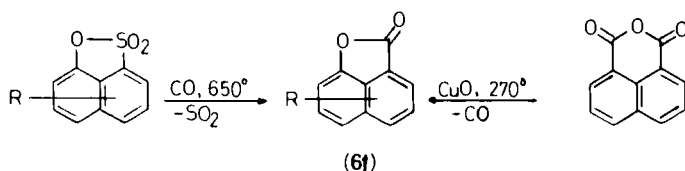
(78BCJ657). The syntheses of 3,4,5-trihydronaphtho[*bc*]furans **69** ( $R' = \text{Alk, Ar, OH}$ ) and **70** from 8-hydroxytetralones **67** have been described in a number of papers [64BSF2112; 74BCJ485; 75BCJ1249; 82BCJ865; 83BCJ184; 85JCS(P1)1001; 86JHC657]. Tetralones **67** are first alkylated with  $\alpha$ -halogeno derivatives of carbonyl compounds, and then the products **68** undergo cyclodehydration.



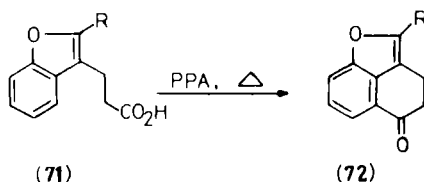
On pyrolysis of naphthosultone in a carbon dioxide atmosphere



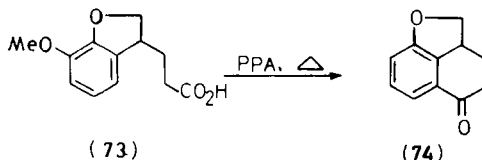
(71TL4093) or of naphthalic anhydride in the presence of cupric oxide (82GEP3105485), naphtholactones **61** have been obtained.



b. *Syntheses from Benzo[*b*]furan Derivatives.* Benzofurans **71**, in which position 2 is blocked with a substituent and a propionic acid fragment is attached to position 3, undergo the intramolecular C-acylation to give 3,4-dihydronaphtho[*bc*]furan-5-ones **72** (67BSF2405). This reaction



proceeds slowly, and product **72** is obtained in low yield. This is explained [72JCS(P1)860; 82HCA1837] by strain in **72** that makes the heterocyclization more difficult. However, the hydration of a 2,3 bond in this benzofuran facilitates the further cyclization, for instance, of **73**→**74** (78BCJ2068).



## 2. Naphtho[*bc*]thiophenes

a. *Attachment of a Heterocycle to Naphthalene or Anthracene Nuclei.* One of the variants of the thiophene ring-addition is based on the formation of a bond between the peri-situated carbon and sulfur atoms. An

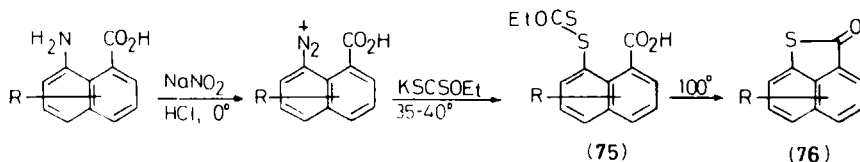
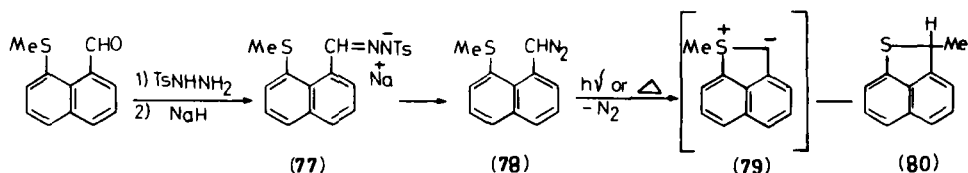
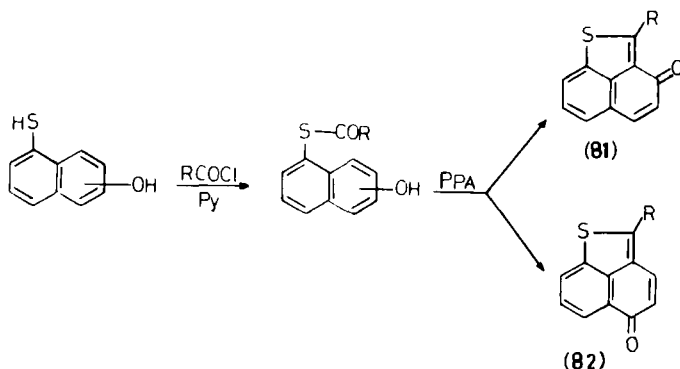


illustration of this principle is the synthesis of naphtho[*bc*]thiophene-2-ones **76** by cyclization of 8-ethoxythiocarbonylmercaptanaphthoic acids **75**. The latter compounds are synthesized from peri-naphthoic acids by the Sandmeyer reaction [12LA(388)1; 38JA2255; 66AJC1909].

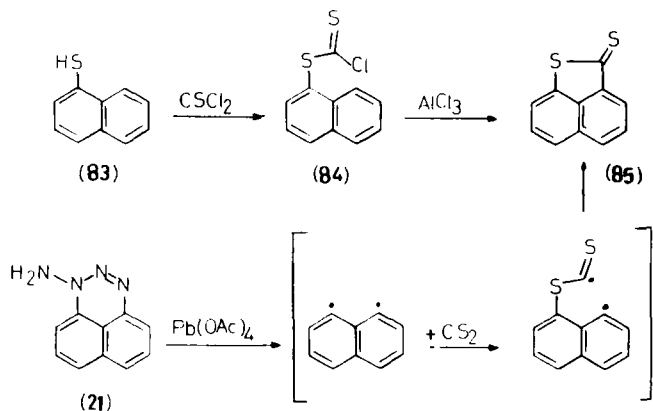
On photolysis or thermolysis of the peri-methylmercapto-substituted sodium salt of  $\alpha$ -naphthaldehyde tosyl hydrazone **77** or diazomethylnaphthalene **78**, 2*H*-2-methylnaphtho[*bc*]thiophene **80** (83JA6096) is formed in 20% yield. Ylid **79** may be a predecessor of thiophene **80**. In



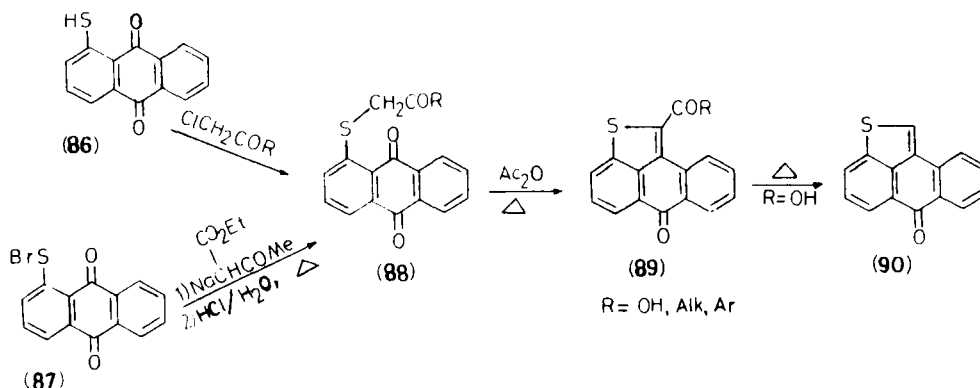
another variant, the thiophene ring is closed by attack of the carbon atom of an  $\alpha$ -acyl or  $\alpha$ -thioacylmercapto group on the neighboring peri-position. Thus, 8-acylmercaptanaphthalenes having a 2- or 4-hydroxy group that activates the 1-position in the naphthalene nucleus, are converted into naphtho[*bc*]thiophenones **81** and **82** in polyphosphoric acid (81AP91, 81CZ89).



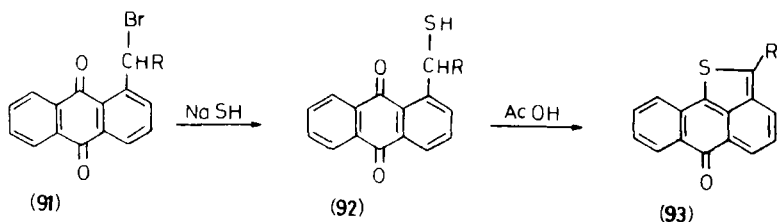
Reaction of naphthalene-1-thiol **83** with thiophosgene gave compound **84**, which was treated with aluminum chloride to give naphtho[*bc*]thiophene-2-thione **85**. This compound was formed also on oxidation of 1-aminonaphtho[*de*]triazine **85** in carbon disulfide [81JCS(P1)413]. Closure of a thiophene ring with formation of naphtho[*bc*]thiophene benzologs (so-called thiopheneanthrones **89**) occurs on heating 1-carboxy or 1-acylmethylmercaptoanthraquinones **88** in acetic anhydride. Anthraquinones **88** have been obtained by reacting anthraquinone-1-thiols **86** with  $\alpha$ -chlorocarbonyl compounds or 1-anthraquinonylsulphenyl bromide **87**



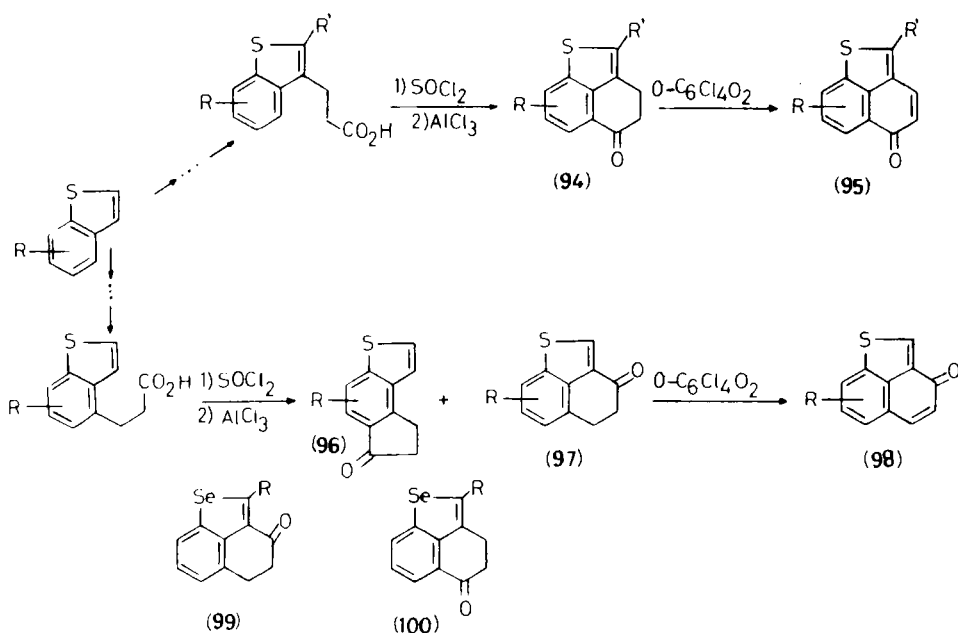
with the sodium salt of acetoacetic ester [12LA(393)113; 69M905; 70M544; 79JOC2491, 79HOV414].



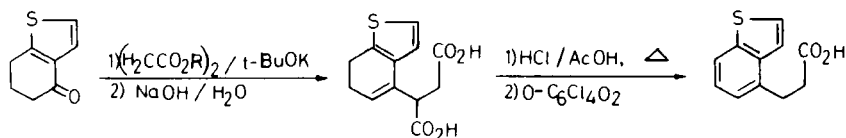
Thiopheneanthrones with a carboxy group in the  $\alpha$ -position of the thiophene ring are easily decarboxylated to  $\alpha$ -unsubstituted heterocycles **90**. Peri-annulated heterocyclic systems with a 1,10-anthraquinonoid structure **93** ( $\text{R} = \text{H, CO}_2\text{H}$ ) are obtained by cyclization of 1-thiolomethyl or 1-thiolocarboxymethylantraquinones **92**, formed on interaction of the corresponding bromoanthraquinone derivatives **91** with thiourea or sodium hydrosulfide (80MI3; 82ZOR1781; 84ZOR1553).



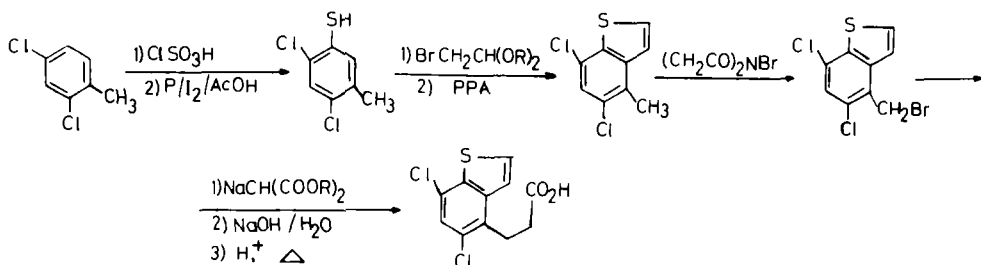
b. *Attachment of a Carbocyclic Fragment to the Benzo[b]thiophene Nucleus.* The most general pathway to the naphtho[bc]thiophene nucleus implies introduction of the propionic acid fragment to position 3 or 4 in benzo[b]thiophene through a number of stages, followed by intramolecular C-acylation to 3,4- or 4,5-dihydronaphtho[bc]thiophenes **94** [66AJC1909; 70JHC107; 76AG810; 76AG(E)775; 80M11] and **97** (66AJC1909; 77LA904) This approach was applied to the synthesis of dihydronaphtho[bc]selenophenones **99** and **100** (74BCF681; 81AP91).



If a blocking substituent is situated ortho to the propionyl fragment, electrophilic attack is directed only to the neighboring peri-position. In the absence of such a substituent, a mixture of ortho- and peri-annelated isomers **96** and **97** has been obtained. On heating with chloranil, dihydro ketones **94** and **97** undergo dehydrogenation to 5- and 3-naphtho[bc]thiophenones **95** and **98**.

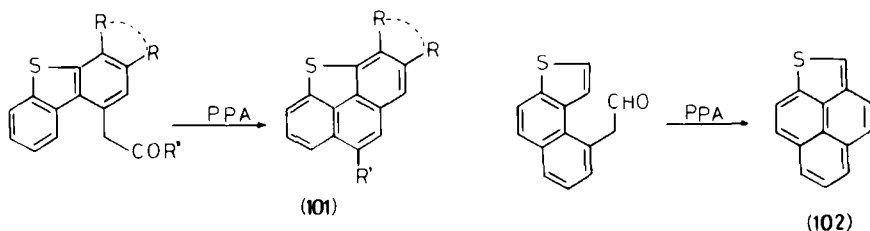


SCHEME 3

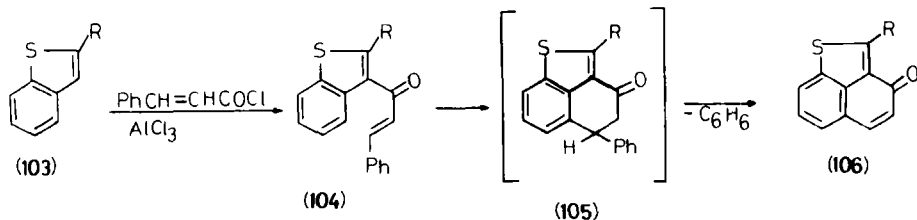


SCHEME 4

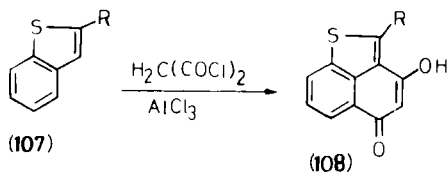
Syntheses of 3- and 4-benzothiophenyl propionic acids were carried out by various routes. Schemes 3 and 4 introduce some of them and describe the formation of two representatives of 4-benzothiophenyl propionic acids (66AJC1909; 77LA904). Intramolecular electrophilic substitution with the goal of attaching a carbocycle was applied also to the syntheses of some polynuclear compounds **101** (83JHC1149, 83JHC1453) and **102** (81JHC977).



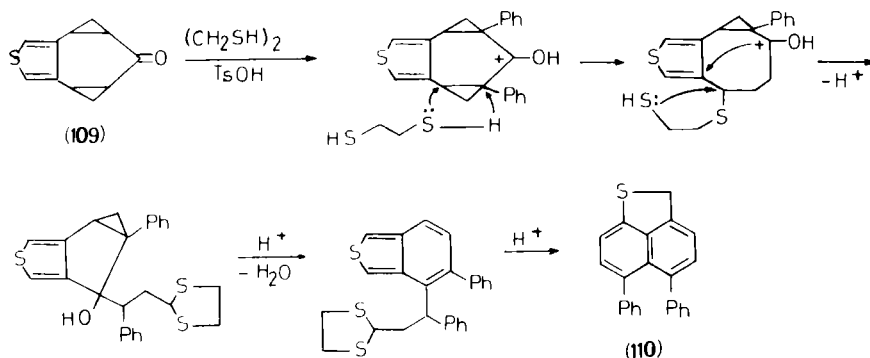
The formation of naphtho[*bc*]thiophene-3-ones **106** takes place on acylation of 2-substituted benzo[*b*]thiophenes **103** with cinnamoyl chloride (78AP710, 78LA627; 79LA965). Interestingly, the aromatization of the intermediate **105** occurs with elimination of benzene. Chalcone **104** also may be obtained on acetylation of benzo[*b*]thiophene **103**, followed by condensation of benzaldehyde with the methyl group of the 3-acetylbenzo[*b*]thiophene intermediate (79LA965).



Naphtho[*bc*]thiophenones **108** can be synthesized in one step on acylation of 2-substituted benzo[*b*]thiophenes **107** with malonic acid



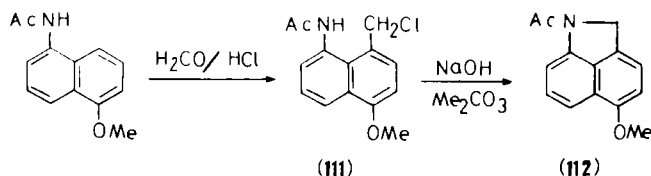
dichloride [77JCR(S)118; 81CZ91]. A chain of amazing rearrangements, followed by formation of 5,6-diphenyl-2H-naphtho[bc]thiophene **110**, takes place on interaction between so-called thiopheno[c]bis-homotropone **109** and ethane dithiol under conditions of acidic catalysis (85CJC2089).



### 3. Benzo[cd]indoles

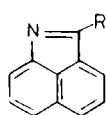
#### a. Syntheses Based on Naphthalene Derivatives.

i. *Heterocyclization of peri-amino-substituted halogeno-methyl and carbonyl naphthalene derivatives.* The simplest route to constructing benzo[bc]indole is closure of the five-membered heterocycle by bond formation between the nitrogen atom of the amino function and the peri-situated electron-deficient carbon atom. Suitable starting materials for such heterocyclizations are peri-amino-substituted halogeno-methyl or carbonyl naphthalene derivatives. Thus 8-acetyl-1-chloromethyl-4-methoxyaminonaphthalene **111**, formed from 1-acetyl-5-

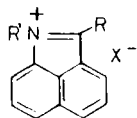


methoxynaphthalene under basic conditions, conditions is converted into *N*-acetyl derivative of 1,2-dihydrobenzo[*cd*]indole **112** (50HCA1797).

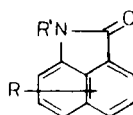
The heterocyclization of peri-aminonaphthoyl compounds allows the preparation of three main types of benzo[*cd*]indole series, namely, bases **113**, benzo[*cd*]indolium salts **114**, and benzo[*cd*]indole-2-ones **115**. Because closure to the nitrogen heterocycle is so facile, peri-amino-substituted naphthaldehydes and naphthyl ketones, even under conditions of their formation, are converted into benzo[*cd*]indoles **113**. Those unsubstituted in position 2, as well as 2-alkyl-substituted benzo[*cd*]indoles **113** ( $R = H, \text{Alk}$ ), have not been isolated because of their easy oxidation by air.



(113)

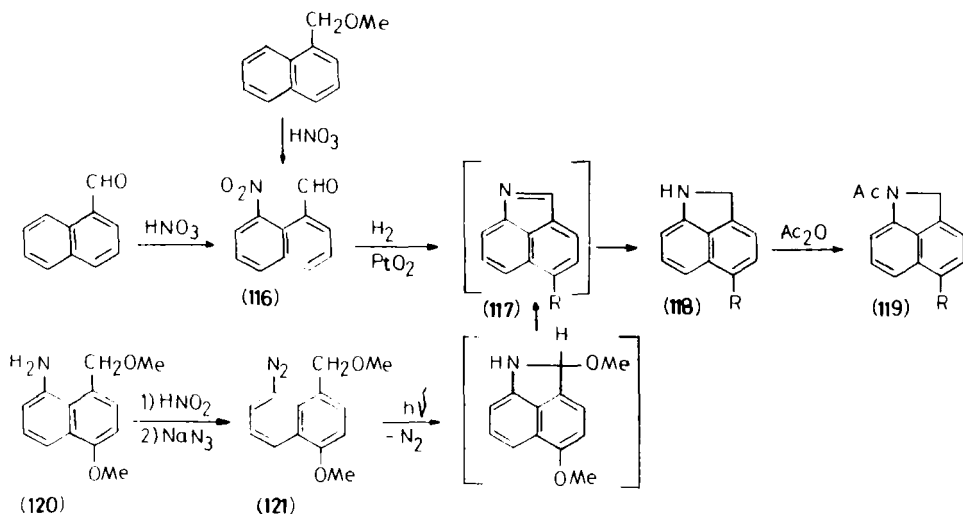


(114)



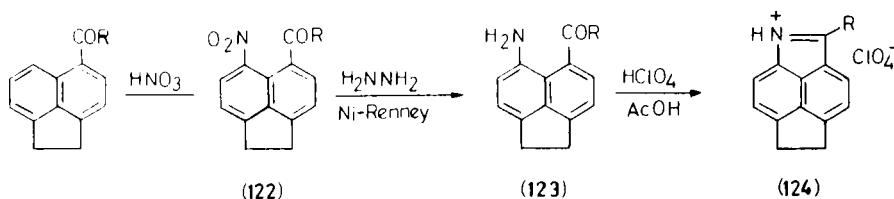
(115)

The reduction by hydrogen and platinum dioxide of 1,8-nitronaphthaldehyde **116**, obtained by the nitration of 1-naphthaldehyde (1888CB256; 40HCA441; 50ZOB1030; 59M634), or 1-methoxymethylnaphthalene (73HCA1382), proceeds obviously via the simplest benzo[*cd*]indole **117** ( $R = H$ ) which, under conditions of the reaction, is reduced to 1,2-dihydrobenzo[*cd*]indole **118** (59M721). On treatment with acetic anhydride, the latter compound gives the stable *N*-acetyl-1,2-dihydrobenzo[*cd*]indole **119** ( $R = H$ ).



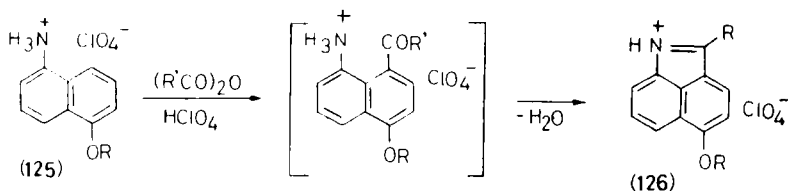
8-Amino-4-methoxy-1-methoxymethylnaphthalene **120**, obtained from the chloromethyl derivative **111**, is transformed into azide **121**. The latter undergoes photolytic heterocyclization to the labile 5-methoxybenzo[*cd*]indole **117** which, on reduction by lithium aluminium hydride followed by acetylation, is converted into the stable 1-acetyl-5-methoxy-1,2-dihydrobenzo[*cd*]indole **119** ( $R = \text{OMe}$ ) [71JCS(C)721]. The reduction of methyl or phenyl 8-nitro-1-naphthyl ketones by hydrogen and platinum dioxide or by iron in acetic acid leads to a mixture of products (59M634).

If acenaphthene derivatives have a bimethylene bridge "pulling" together peri-positions, the closure of the second five-membered ring is hindered, and in this case, the isolation of peri-aminoacenaphthalene ketones **123** (66ZOR148; 68ZOR2002) formed on reduction of peri-nitro ketones **122** (20CB289; 25CB2239; 62MI1; 64BSF646; 68ZOR2002) is possible. Heating acetic acid solutions of peri-amino ketones **123** with perchloric acid gives rise to acenaphtho[4,5-*bc*]pyrrolium salts **124** ( $R = \text{Me, OH}$ ) (89UPI).



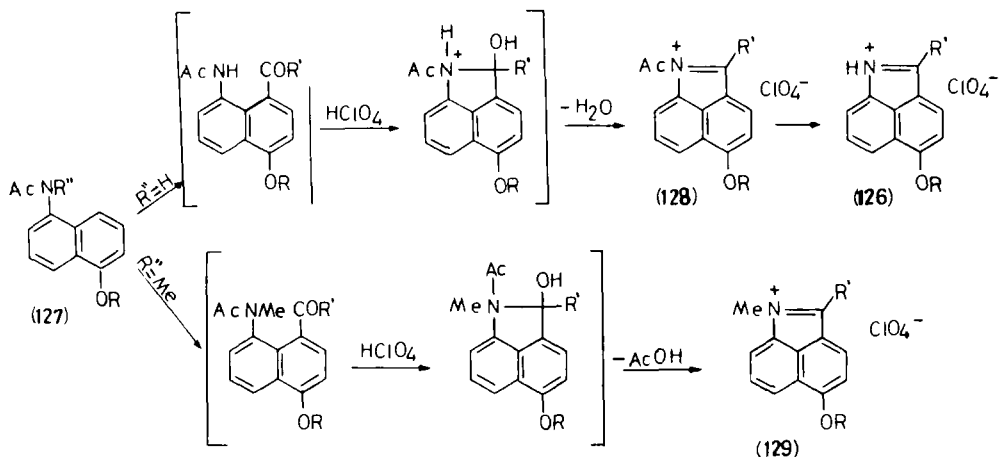
A general method for synthesizing benzo[*cd*]indolium salts is the acid-catalyzed C-acylation of 5-alkoxy-1-aminonaphthalene derivatives. The course of C-acylation, necessary for the formation of the peri-aminocarbonyl group, is determined by the para-orienting effect of a methoxy group in one ring of the naphthalene nucleus and the simultaneous neutralization (N-protonation or N-acylation) of an amino group in the other ring. The conditions of formation of peri-amino-substituted naphthaldehydes and naphthyl ketones are favorable for their conversion into benzo[*cd*]indolium cations.

Thus, on heating perchlorates of 5-alkoxy-1-aminonaphthalene **125** ( $R = \text{Me, Et}$ ) with alkyl carboxylic anhydrides in the presence of catalytic amounts of perchloric acid, N-protonated 2-alkyl-benzo[*cd*]indolium

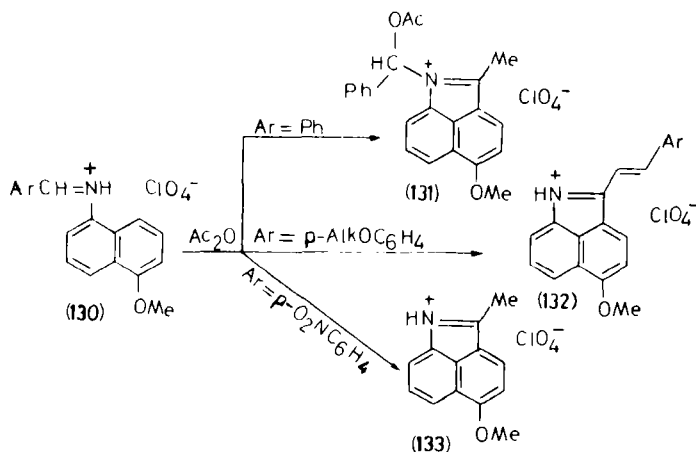




salts **126** have been obtained (80ZOR1958). Acylation of 1-acetylamino-5-alkoxynaphthalenes **127** ( $R'' = H$ ) with aliphatic anhydrides in the presence of perchloric acid (80ZOR1958; 83MI2) or with dichloromethyl ethyl ether (86ZOR2394) or aromatic acid chlorides (81ZOR1998) in the presence of  $AlCl_3$  leads to *N*-acetylbenzo[*cd*]indolium salts **128** ( $R' = H, Alk, Ar$ ). Under the same conditions, 5-alkoxy-1-(*N*-acetyl-*N*-methyl)-aminonaphthalenes **127** ( $R'' = Me$ ) give rise to *N*-methyl-substituted benzo[*cd*]indolium perchlorates **129**. In air or on heating in acetic acid solution, *N*-acetylbenzo[*cd*]indolium perchlorates **128** add a molecule of water, followed by elimination of acetic acid fragments, to afford *N*-protonated benzo[*cd*]indolium perchlorates **126** (80ZOR1958; 81ZOR1998).

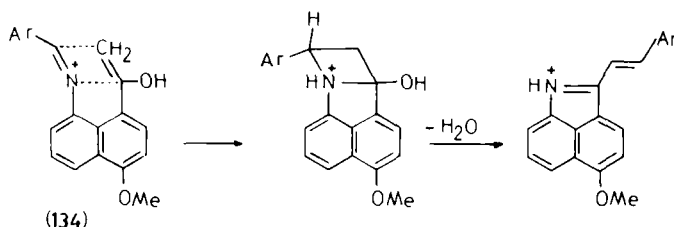


The method just described allows high yields of the various *N*-protonated, *N*-alkylated, and *N*-acylated benzo[*cd*]indolium salts, both



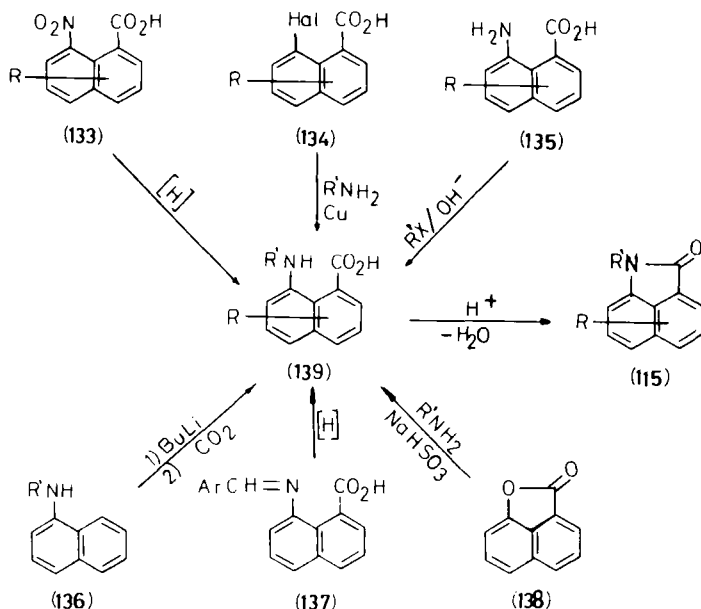
without a substituent in position 2, and 2-alkyl or 2-aryl derivatives **126**, **128**, and **129**. The formation of benzo[*cd*]indolium cations **131**–**133**, which are different in terms of substituents at the nitrogen atom or in position 2, occurs on briefly heating azomethine perchlorates **130** in acetic anhydride (84ZOR225; 85ZOR1941).

The course of reaction and the character of the final products are determined by electronic effects of substituents at the aryl ring (Ar) of N-protonated azomethine **130**. The most interesting is the reaction leading to 2-styrylbenzo[*cd*]indolium salts **132**; the formation of which can be represented as the result of a rearrangement of intermediate **134**. The latter is afforded by C-acylation of azomethine perchlorate **130**.

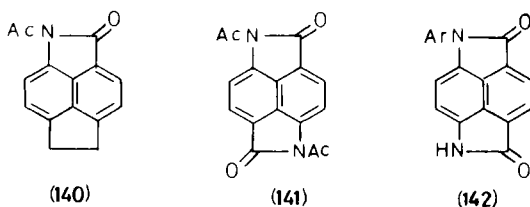


Naphthostyryl **115** ( $R = R' = H$ ) and its numerous N- and naphthalene-substituted derivatives are obtained by acid-catalyzed heterocyclization of peri-aminonaphthoic acids **139**. One should notice it is not necessary to isolate these acids since, as a rule, conditions of their formation are suitable for heteroring closure. Syntheses of benzo[*cd*]indole-2-ones **115** are carried out in a number of ways:

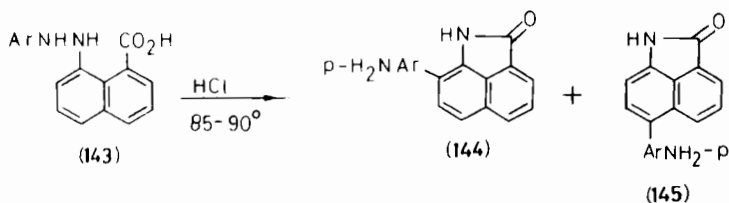
- (1) By reduction of 1,8-nitronaphthoic acids **133** [1885CB73; 1885CB2881; 1886CB1131; 61ZOB1655; 63ZOB2250; 77GEP(O)2649167],
- (2) By interaction of 1,8-halogenonaphthoic acids **134** with ammonia (32JCS175; 33MI1; 34JCS137, 34JCS168; 36MI1, 36MI2; 69ZOR479; 73ZOR1067) and primary amines (35JCS317; 60JCS1537),
- (3) By N-alkylation of 1,8-aminonaphthoic acids **135** in alkaline medium followed by acidification (22HCA560; 23JCS224; 32HCA1366; 59TH1),
- (4) By lithiation of  $\alpha$ -naphthyl amines **136** followed by decarboxylation (62JOC4421; 67JOM171; 69IJC538; 83S953),
- (5) By reduction of azomethines on the basis of 1,8-aminonaphthoic acid **137** (51HCA382),
- (6) By interaction of naphtholactone **138** with amine under Bucherer reaction conditions (83EUP84853).



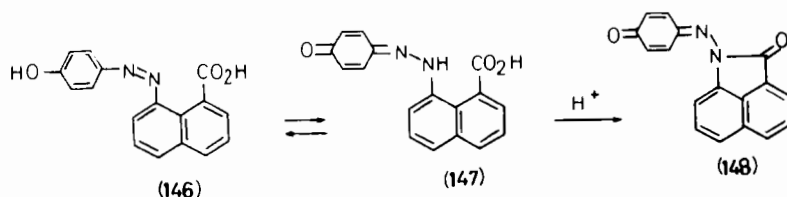
The heterocyclization of peri-aminonaphthoic acids is significantly hindered if the other two carbon peri-atoms are incorporated into the five-membered ring. However, on lengthy heating, the cyclization occurs under fairly severe conditions. Thus, boiling 4,5-aminoacenaphthoic acid or 5-amino-6-carboxynaphthostyryl in acetic anhydride gives rise to compounds **140** (68DOK852) or **141** (75ZOR1731), and heating 6-bromo-5-carboxynaphthostyryl with aryl amines leads to bis-lactam **142** [581JC(B)377].



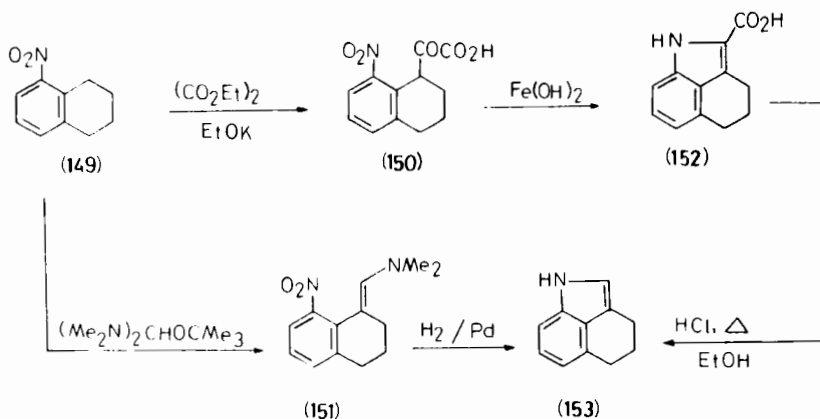
Representatives of 1,8-aminonaphthoic acids having a fragment of aryl hydrazine as the amine function (**143**) are cyclized in acidic medium on heating. This process is accompanied by the benzidine rearrangement, resulting in the mixture of aminoaryl-substituted naphthostyryls **144** and **145** with the predominance of ortho-isomer **144** (63ZOB974, 63ZOB3105).



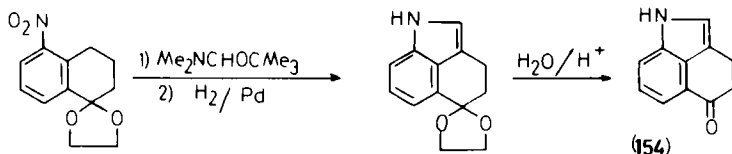
Peri-carboxy-substituted diazophenols **146**, which are able to form a peri-aminocarbonyl fragment **147** as a result of protonation in acidic medium, are converted into *N,N*-derivatives of naphthostyryl **148**



(30GEP496340). This approach to construction of the benzo[*cd*]indole nucleus is extended to the syntheses of their partially hydrogenated derivatives. Thus, 2-nitrotetralin **149** is converted into 1,8-nitrocarbonyl or dimethylaminomethylene derivatives **150** and **151**, the reduction of which gives rise to 1,3,4,5-tetrahydrobenzo[*cd*]indoles **152** and **153** (55JA3334; 84TL285).

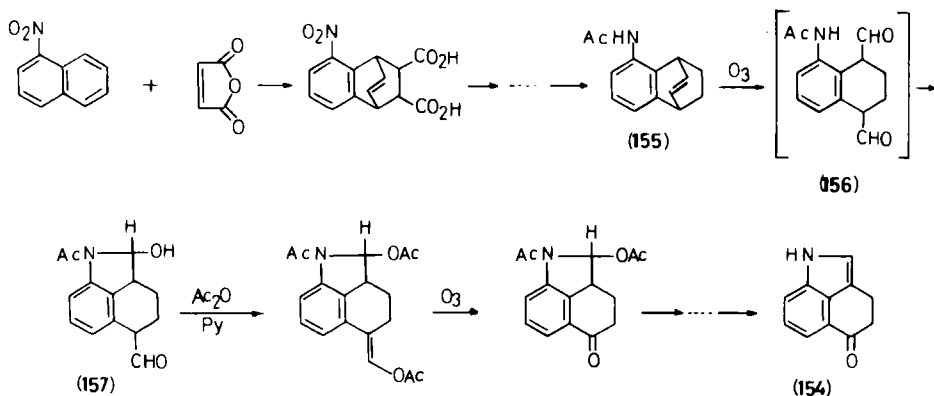


Condensations of 5-nitrotetralin with diethyl oxalate (**149** → **150**) or *tert*-butoxy-bis-dimethylaminomethane (**149** → **151**) are possible because of the activation of the methylene link by the ortho-situated nitro group. The dimethylaminomethylenation reaction (**149** → **151**) was also applied



to synthesis of 1,3,4-trihydrobenzo[*cd*]indole-5-one (Uhle ketone) **154** (84TL285), which is a key intermediate in the synthesis of lisergine alkaloids.

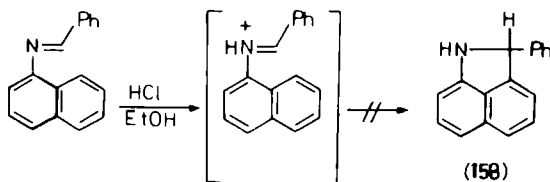
Plieninger and co-workers (62T267; 67CB2427; 76CB2122, 76CB2126; 76CB2140) have found a nontrivial pathway for transforming the naphthalene nucleus into benzo[*cd*]indole. A key step is the [4 + 2] cycloaddition of an olefinic component to  $\alpha$ -nitronaphthalene, playing the role of diene, followed by reduction of the nitro group and oxidation of the alkylidene bridge to aldehyde groups (**155**  $\rightarrow$  **156**). The aldehyde and peri-amino groups are closed to the five-membered heteroring (**156**  $\rightarrow$  **157**).



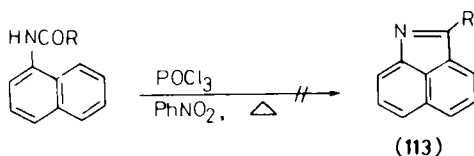
The synthesis of the Uhle ketone **154** by this method is given in the following structures as an example. Various polyhydrobenzo[*cd*]indoles, including some natural products, have been obtained by this way.

ii. *Cyclization of 1-acylaminonaphthalenes and their derivatives.* A very attractive approach to the benzo[*cd*]indole nucleus is based on the intramolecular attack of a peri-position by the electron-deficient carbon atom attached to the nitrogen atom of  $\alpha$ -naphthylamine. Depending on the oxidation state of the electron-deficient carbon atom, 1,2-dihydrobenzo[*cd*]indole or benzo[*cd*]indole-2-one derivatives must be formed. However, not all attempts were successful.

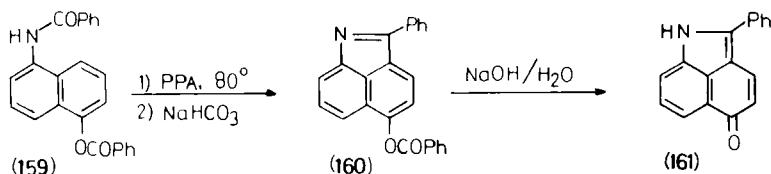
The synthesis of 2-phenyl-1,2-dihydrobenzo[*cd*]indole **158**, on boiling benzylidene  $\alpha$ -naphthyl-amine with hydrochloric acid in ethanol, was re-



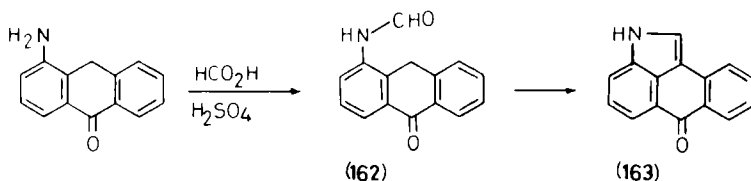
ported (78ZOR1340). However, subsequent data showed (81MI1) this reaction provided a mixture of compounds, none of which was the desired benzo[*cd*]indole derivative. The information about the synthesis of 2-substituted benzo[*cd*]indoles **113** (R = Alk, Ar) on heating  $\alpha$ -acylamino-naphthalenes with phosphorus oxychloride in nitrobenzene was also mistaken (73KGS49). As in the previous case, the mixture was obtained also without benzo[*cd*]indoles **113** (81MI1).



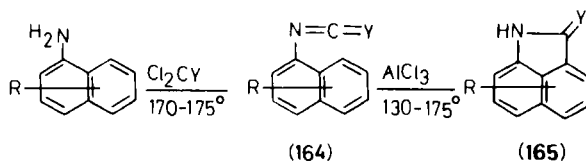
It is possible to reach the desired result by introducing a para-orienting substituent in position 5 of 1-acylamino-naphthalenes. Indeed, heating 1-benzoylamino-5-benzoyloxynaphthalene **159** in polyphosphoric acid leads to 5-benzoyloxy-2-phenyl-benzo[*cd*]indole **160** which, on alkaline heating, gives rise to 2-phenylbenzo[*cd*]indole-5-one **161** (80AP977).



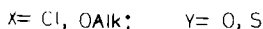
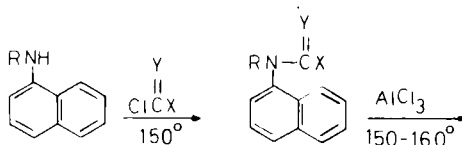
The interaction of 1-aminoanthrone with formic acid in the presence of sulfuric acid leads to N-formylation and to formation of 1-formyl-aminoanthrone **162**, which is cyclized under these conditions into pyrroloanthrone **163** (79HOU414). The application of this approach was found especially fruitful for heterocyclization of  $\alpha$ -naphthylamine and carbonic



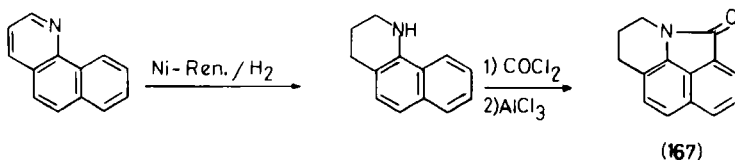
acid derivatives. Heating  $\alpha$ -naphthylamines with phosgene or thiophosgene in trichlorobenzene gives rise to  $\alpha$ -naphthylisocyanates or their thio analogs **164**, which then are cyclized into the corresponding benzo[*cd*]indole-2-ones **165** (Y = O) or benzo[*cd*]indole-2-thiones **165** (Y = S) by the action of  $\text{AlCl}_3$  in halogenobenzene solutions at 130–180°C [51DOK1073, 51USP2628964; 53ZOB798; 54ZOB1871; 78GEP(O)2635693, 78GEP(O)2700649].



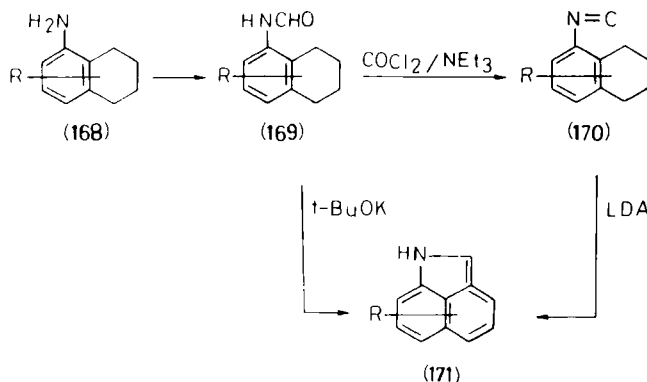
The purity of naphthostyryl obtained by this method in a yield of 80% is very high (**99**, 7%) [78GEP(O)2635693, 78GEP(O)2700649]. Under analogous conditions, *N*-alkyl-substituted naphthostyryls **166** (R = Alk, Y = O) or their thio analogs **166** (R = Alk, Y = S) are obtained from mono-*N*-alkyl derivatives of  $\alpha$ -naphthylamine and phosgene (62SZ



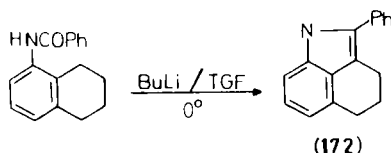
P422798; 63BEP622565; 64BRP973260, 64FRP1344966, 64MIP1; 73GEP1295555; 86URP1114678), thiophosgene [77JCR(M)882], or chloro-carbonic esters [85GEP(O)3443994]. Several patents have been registered for those methods of synthesizing *N*-alkylnaphthostyryl derivatives **167** in which the *N*-alkyl group is the fragment of a carbocycle (65BEP662236, 65BEP662237, 65BRP1064605, 65NEP6504566; 68SZP456812).



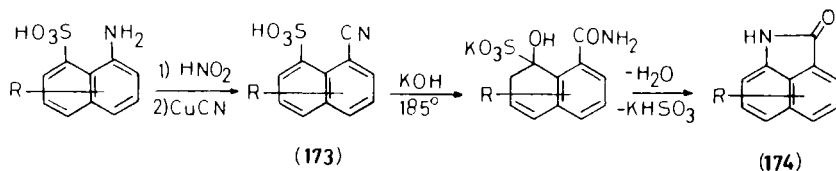
A method for synthesizing 1,3,4,5-tetrahydrobenzo[*cd*]indoles **171** from 2-aminotetralins **168**, which were first formylated by formic acid or *N*-formylimidazole, was described. The 2-formyltetralins thus formed were



cyclized by the action of potassium *tert*-butoxide (55JA3334) or on treatment with a mixture of phosgene and triethylamine, followed by addition of lithium diisopropylamide (via isonitrile **170**) (84TL289). Analogously, the action of butyl lithium converts 2-benzoylamino-tetralin into 2-phenyl-1,3,4,5-tetrahydrobenzo[*cd*]indole **172** (81JOC4511).



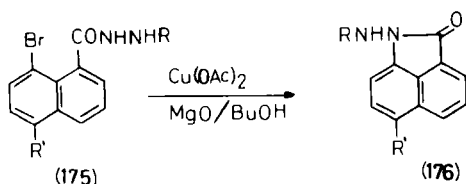
iii. *Heterocyclization of peri-substituted carboxoamides or aminoalkyl compounds.* One of the schemes for constructing the benzo[*cd*]indole nucleus is based on the intramolecular change of a functional group by the nitrogen atom belonging to the peri-situated carboxoamide or aminoalkyl group. This principle is applied to the synthesis of naphthostyryl and its derivatives **174** (R = H, OH, Hal), formed on alkaline fusion of 1,8-cyanonaphthalene sulfonic acid **173** (27BRP276126, 27GEP441225, 27GEP444325, 27GEP452063, 27USP1646290; 28GEP459404; 31GEP-516678, 31GEP531889; 50HCA1955; 51HCA382; 63MI1; 66MI1; 70CRV439).



The description of the commercial synthesis of naphthostyryl from 1,8-cyanonaphthalenesulfonic acid is reported in the monograph by



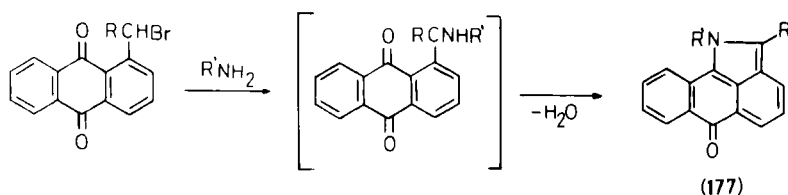
Donaldson (63MI1). On heating in the presence of copper salts, 1,8-bromonaphthoic acid hydrazides **175** are cyclized into N,N-derivatives of naphthostyryl **176** (62ZOB1332; 63ZOB680, 63ZOB2712, 63ZOB3105).



R = H, Ar, COAr

R' = H, Br

The described principle of heterocyclization was applied to the synthesis of pyrroloanthrones **177**, having the 1,10-anthraquinonoid structure (81ZOR1558; 83MI1; 84ZOR1553).

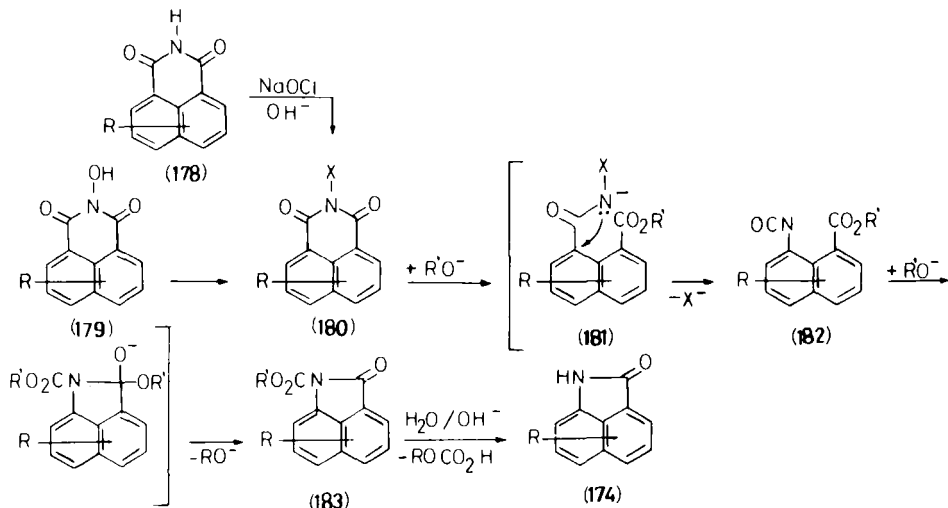


R = H, CO<sub>2</sub>Me

R' = H, Alk, Ar

iv. *Construction of benzo[cd]indole nucleus from naphthaloimide derivatives.* The general principle of synthesizing naphthostyryl and its derivatives **174** is based on oxidation of naphthaloimides **178** in the Hofmann reaction [06CB(42)2336; 10CB439; 11BSF86; 22HCA560; 54MI1; 55ZOB2485; 57MI1; 61MI1] or on rearrangement of *N*-dinitrophenyloxy (74ZOR2232; 77ZOR2194) and *N*-acyloxy- [55MI1; 66JCS(C)523; 70ZOR-1480; 72ZOR165; 73ZOR171; 75GEP2417789; 76ZOR1057, 76ZOR-1787; 77GEP2628653; 81TH1, 81ZOR1013] naphthaloimides **180b-e** by the action of bases (alkali metal hydroxides, alcoholates, and amines). The sequence of transformations in these cases may be depicted in Scheme 5.

It was assumed that the rearrangement of *N*-anionic intermediate **181** into isocyanate **182** occurs as a synchronous process including the formation of a new C—N bond and the withdrawal of the anion acid (X<sup>-</sup>), but without formation of the intermediate nitrene. According to early papers, information about yields of naphthostyryl **174** (R = H), which is obtained from naphthaloimide **178** (R = H) by the Hofmann reaction, is contradictory. The procedure has been checked and developed preparatively by



SCHEME 5.  $\text{X} = \text{Cl}; \text{OC}_6\text{H}_3(\text{NO}_2)_2; \text{RCO}_2; \text{ArSO}_3; (\text{RO})_2\text{PO}_2$ .

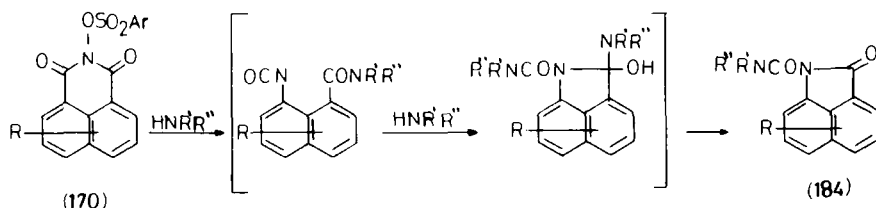
M. M. Dashevskii. The description of this experimental method for naphthostyryl (yields 89–90%) is given in the monograph (66MI1).

The conversion of *N*-acyloxynaphthaloimides **180c–e** into naphthostyryls **174** by the action of alkaline agents is accompanied as a rule by deacylation of the former compounds to *N*-hydroxynaphthaloimides **179**. These competing processes are influenced by the nature of substituents at the nitrogen atom and the naphthalene nucleus. It was shown that unsubstituted *N*-acetoxy- and *N*-benzoyloxynaphthaloimides **180** ( $\text{R} = \text{H}$ ,  $\text{X} = \text{OAc}$ ,  $\text{OBz}$ ) undergo only the cleavage of an ester group, resulting in *N*-oxide **179** ( $\text{R} = \text{H}$ ), whereas the presence of at least one substituent at the naphthalene nucleus of **180** ( $\text{R} \neq \text{H}$ ) promotes the formation of corresponding naphthostyryl derivatives **174** ( $\text{R} \neq \text{H}$ ). If the electron-withdrawing substituent is attached to position 5 in *N*-acyloxynaphthaloimide **180c** (para-position towards a carbonyl group), 5-substituted naphthostyryls **174** ( $\text{R} = \text{Br}$ ,  $\text{NO}_2$ ,  $\text{SO}_3\text{H}$ ,  $\text{CO}_2\text{H}$ ) are formed, whereas the electron-donor substituent in the same position promotes the formation of 6-substituted naphthostyryls **174** ( $\text{R} = \text{OAlk}$ ). Independent of the nature of the substituent, 3- or 4-substituted *N*-acyloxynaphthaloimides **180c** give rise to the mixtures of 3- and 8- or 4- and 7-substituted isomeric pairs of naphthostyryls **174**, respectively. The substituents at the benzenoid ring of the *N*-aryloxy group also influence yields of naphthostyryls from *N*-aryloxynaphthaloimides **180** ( $\text{X} = \text{ArCO}_2$ ). Moreover, the acceptor substituents facilitate nucleophilic attack on the carbon atom of an ester group

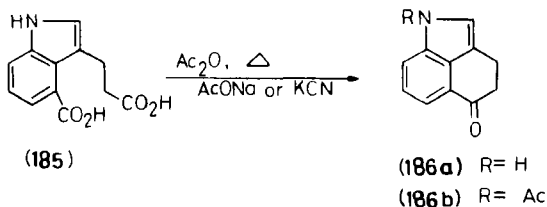
and thus promote the fission of a C—O bond (**180** → **179**). That leads to decreasing yields of naphthostyryls **174**.

*N*-Sulphoxy derivatives **180d** are the most suitable compounds for a preparative synthesis of naphthostyryls from *N*-acyloxynaphthalimides. In this case, the alkaline fission (**180** → **179**) does not occur at all or takes place to a small extent in which yields of the desired products **174** reach 80–90%. The best experimental conditions occur in treatment of *N*-arylsulfoxynaphthalimides **180d** with bases in alcohol solutions. For these cases, it was shown that the excess alkali hydroxide in methanol leads to naphthostyryls **174**, whereas the equimolar ratio of alkali hydroxide or triethylamine in alcohol at room temperature allows the reaction to stop at the formation of *N*-alkoxycarbonyl derivatives **183** (*R*' is a fragment of the used alcohol) (74ZOR2232; 76ZOR1057; 81ZOR1013).

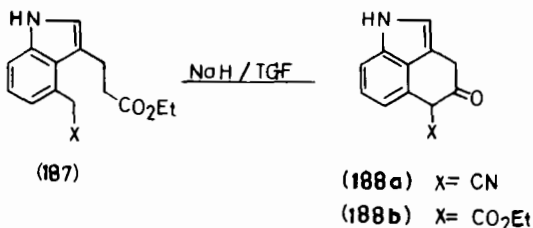
If ammonia or primary or secondary amines were used instead of tertiary amines in organic solvents (alcohol, acetone, chloroform, and dimethylsulfoxide), *N*-arylsulfoxynaphthalimides **180c** gave rise to *N*-carbamoyl derivatives of naphthostyryl **184** (81ZOR1013). For the laboratory synthesis of naphthostyryls, one can recommend also the reaction of *N*-(2,4-dinitrophenyl)oxynaphthalimide **180b** with alkali hydroxides; yields of the desired products **174** are almost quantitative (77ZOR2194).



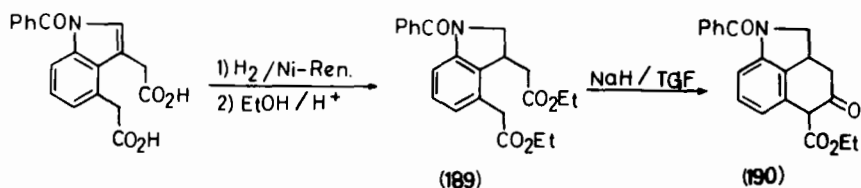
**b. Attachment of a Carbocyclic Fragment to an Indole Nucleus.** For closure to the six-membered carbocycle, one can use the Diekmann condensation or the intramolecular Friedel–Crafts C-acylation and C-alkylation reactions. Heating 4-carboxy-3-indolylpropionic acid **175** with sodium acetate or potassium cyanide in acetic anhydride gives rise to the corresponding 1,3,4-trihydrobenzo[*cd*]indole **186a** (49JA761) and its *N*-acetyl derivative **186b** [72JCS(P1)1121; 80JOC4236].



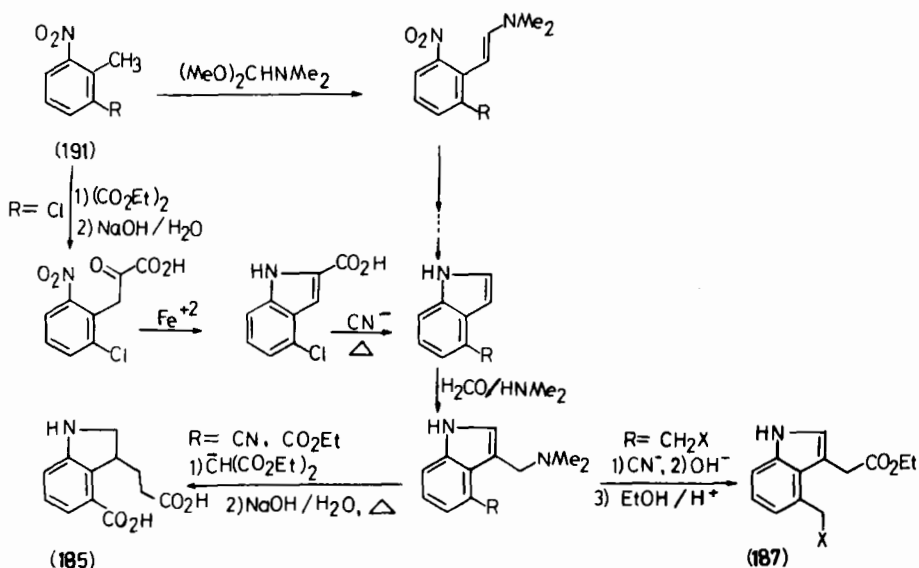
The cyclization of 4-cyanomethyl or 4-carbethoxymethyl-substituted 3-indolylpropionic acids **187** by the action of sodium hydride in tetrahydrofuran leads to 5-substituted 1,3,5-trihydrobenzo[*cd*]indoles **188a,b**



(60CB209). The analogous cyclization is characteristic also of 2,3-dihydroindole derivatives (**189**  $\rightarrow$  **190**) (60CB209).

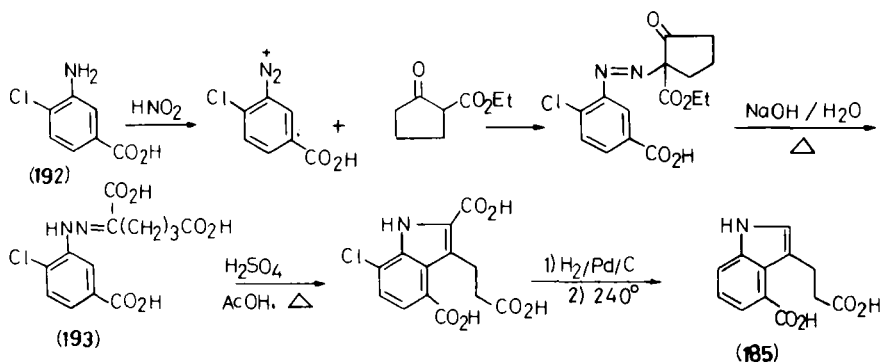


The initial indole derivatives **185** and **187** are synthesized from *ortho*-nitrotoluenes **191** (57CB1980; 60CB2024; 79JOC4003). Indolylcarboxylic

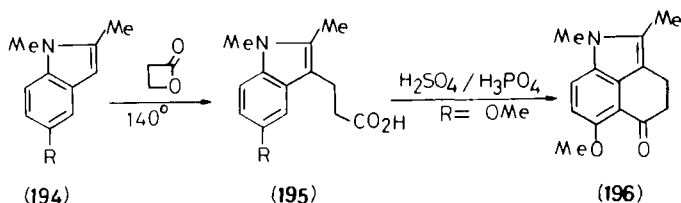


acid **185** is obtained also by the Fischer reaction from the precursor **193**

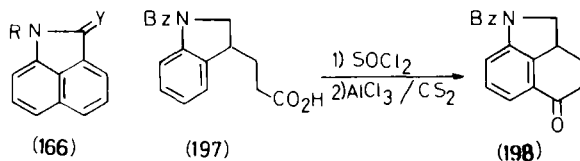
synthesized on the basis of 3-amino-4-chlorobenzoic acid **192** [72 JCS(P1)1121; 80JOC4236].



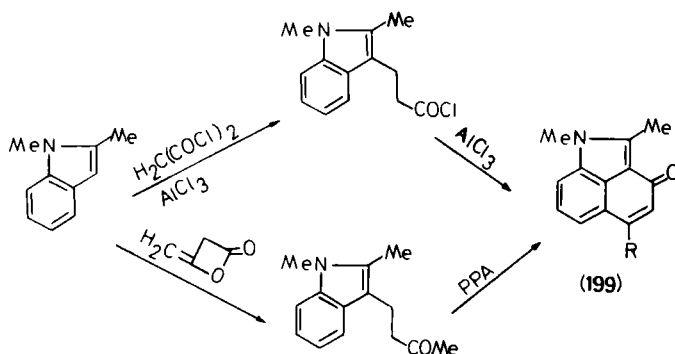
The interaction of 1,2-dimethylindoles **194** ( $\text{R} = \text{H}, \text{OMe}$ ) with proliolactone gives rise to 3-indolylpropionic acids **195** ( $\text{R} = \text{H}, \text{OMe}$ ) and, on treatment with a mixture of sulfuric and phosphoric acids, only the 5-methoxy-derivative for this series can be transformed into 1,3,4-trihydrobenzo[*cd*]indole-5-one **196**, whereas in the absence of an activating substituent (**195**,  $\text{R} = \text{H}$ ), the cyclization does not take place [53CI(L)823; 80LA971].



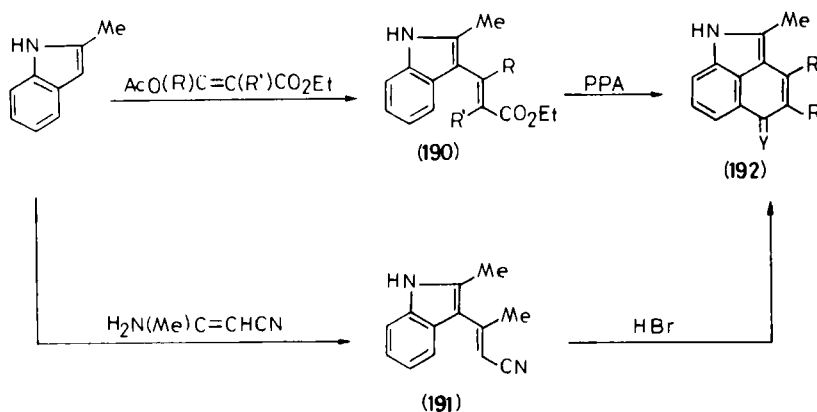
The intramolecular C-acylation into position 4 becomes possible after hydrogenation of the  $\text{C}_2\text{—C}_3$  bond in the indole nucleus. Thus, by the action of aluminum chloride, 1-benzoyl-2,3-dihydroindolylpropionyl chloride **197** is converted into pentahydrobenzo[*cd*]indolone **198** (54JA5256; 56JA3087). Intramolecular electrophilic substitution is favored also by conjugation between a carbonyl or a nitrile group at the  $\beta$ -substituent containing three carbon atoms and the indole nucleus.



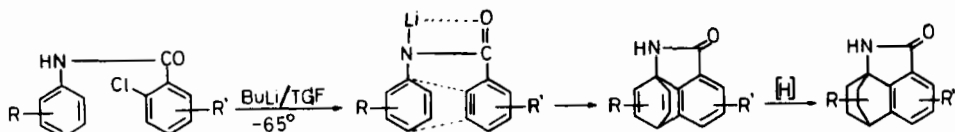
Interaction of 1,2-dimethylindole with malonyl chloride or diketene gives 1,2,5-tri-substituted benzo[*cd*]indole-3-ones **199** (78S685; 80LA971).



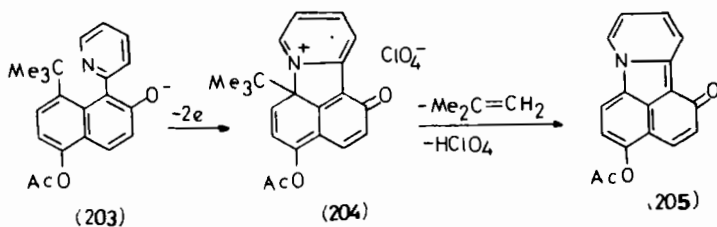
Cyclization of 3-indolylacrylic acid derivatives **200** and **201**, obtained on interaction of 2-methylindole with the enol acetate of acetoacetic ester or with  $\beta$ -amino- $\beta$ -methylacrylonitrile, leads to benzo[*cd*]indole-5-ones **202** ( $Y = O$ ) or their nitrogen analogs **202** ( $Y = NH$ ) (78TL4051).



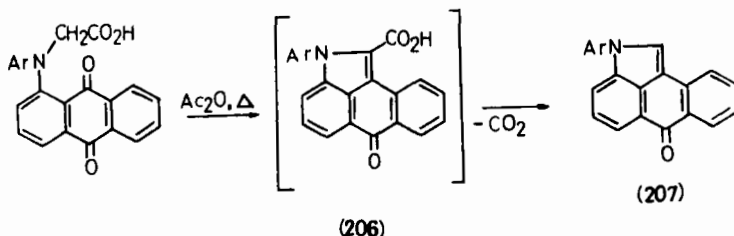
*c. Other Methods of Constructing the Benzo[*cd*]indole Nucleus.* A new approach to the formation of the benzo[*cd*]indole skeleton through the intramolecular conversions of the substituted anilides of *ortho*-chlorobenzoic acids by the action of lithium butylide (81JOC4515) is presented in Scheme 6. The original course of heterocyclization was noted on anodic oxidation of *peri-tert*-butyl-substituted  $\alpha$ -pyridynaphthalene **203** (72 JOC3058). The product of cyclization was isolated as perchlorate **204**; however, it slowly eliminated isobutylene and perchloric acid and was converted into pyridinobenzo[*cd*]indolone **205**.



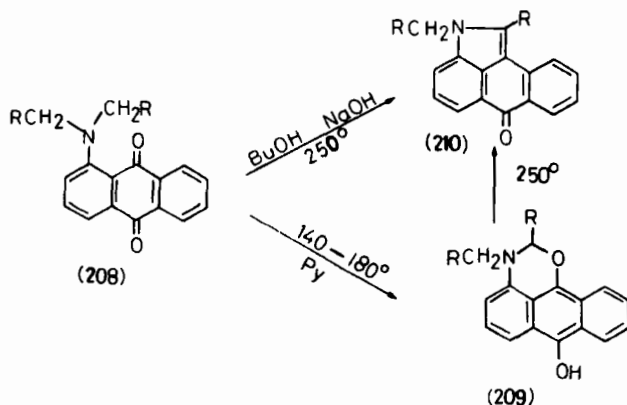
SCHEME 6



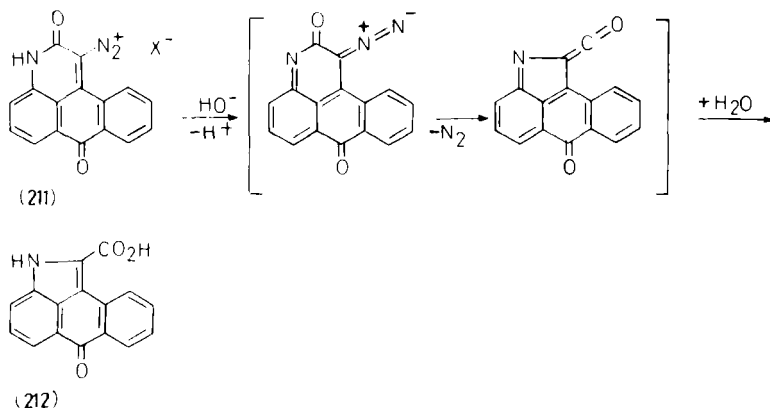
The intramolecular Diekmann-type reaction occurs on boiling 1-aminoanthraquinonyl acetic acid derivatives in acetic anhydride, and it results in 2-carboxypyrroloanthrones **206**, which are decarboxylated under these conditions to 2-unsubstituted pyrroloanthrones **207**



(79HOU414). On heating 1-dialkylaminoanthraquinones **208** at 140–180°C, anthroxazines **209** are formed. At more elevated temperatures, the latter compounds are converted into pyrroloanthrones **210** (75KGS1360), which can be obtained in one step on heating 1-dialkylaminoanthraquinones at 250°C.



Dibenzyl derivatives **208** ( $R = Ph$ ) are converted into pyrroloanthrones **210** ( $R = Ph$ ) under milder conditions (81CL1789). The ring contraction of anthrapyridonyl diazonium salts **211**, which takes place in water in the presence of alkaline agents, leads to 2-carboxypyrroloanthrone **212** (77KGS1103).



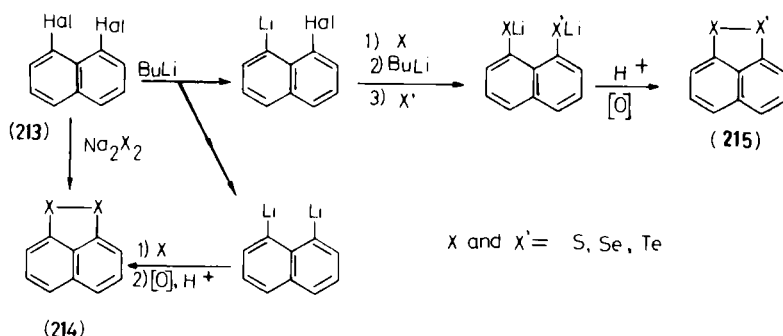
### C. PERI-HETEROCYCLES WITH FIVE-MEMBERED HETERORING AND TWO HETEROATOMS

#### 1. Heterocyclic Systems with Heteroatoms of the Same Name

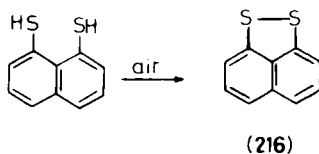
a. *Naphtho[cd]dichalcogenols*. Peri-annelated heterocycles **III** with 1,2-heteroatoms of chalcogenes (S, Se, Te) are interesting because of the augmented  $\pi$ -donor properties, and because of this fact, these compounds are used in studies of metal conductivity ("organic metals"). Such substances are deeply colored, which is explained by the high delocalization of the  $3p$ -electrons of an  $X-X$  group and formation of the  $\pi$ -system common with the naphthalene nucleus.

There are two general approaches to constructing the five-membered 1,2-dichalcogene peri-annelated heteroring. One of them is based on the interaction of 1,8-dihalogenonaphthalenes **213** with alkali dichalcogenides (79ZOR391; 84M11; 86CL551; 87CL315); the other pathway is the reaction of 1,8-dihalogenonaphthalenes with lithium followed by interaction with chalcogenes (77JA255, 77JA7743; 80TL4565). The second approach has more variations than the first, since it allows reactions with lithium and chalcogenes in separate stages and thus provides the desired products either with the same (**214**) or different (**215**) chalcogene atoms.

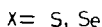
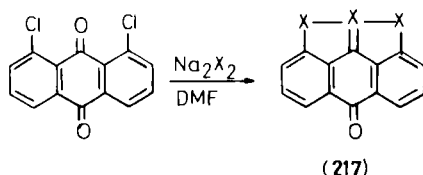




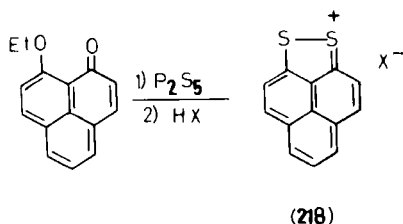
Following interaction between lithiated naphthalene derivatives and chalcogene, heteroring closure requires the participation of an oxidant. In this case, oxygen of the air may play such a role. On air oxidation, 1,8-dithionaphthol is converted into naphtho[cd]dithiol **216** (65JOC3997).



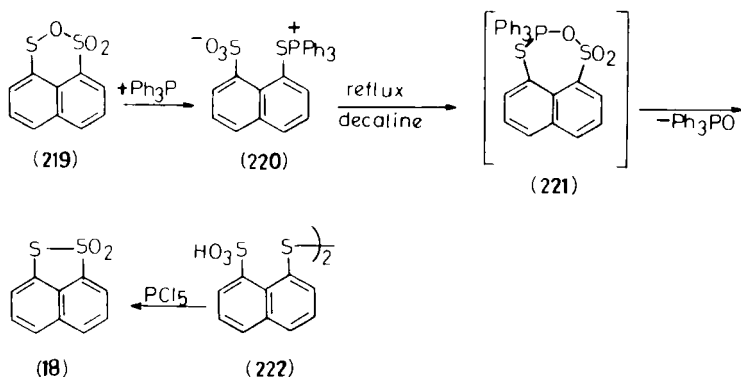
Heating 1,8-dichloroanthraquinone with sodium disulfide or diselenide in dimethylformamide (DMF) leads to pentacyclic systems **217** [78IJC(B)673]. The formation of heterocyclic systems of type **217** and



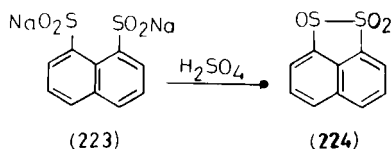
more complex types occurs on heating aromatic polynuclear hydrocarbons (naphthacene, pentacene, etc.) with sulfur or selenium, for instance [72JCS(P1)1310; 73USP3769276]. On heating 9-ethoxyphenalene with phosphorus pentasulfide, followed by treatment with acid, phenaleno[cd]dithiolium salt **218** has been obtained (78CC1429).



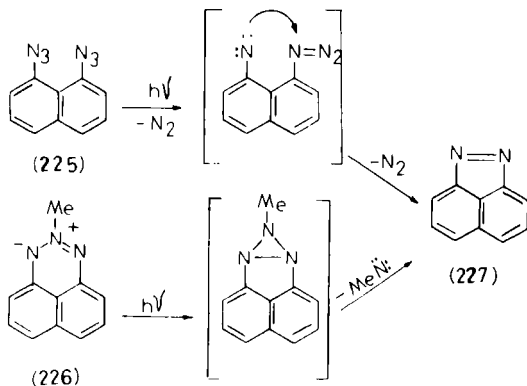
Naphtho[*de*]-2,1,3-oxadithiine *S,S*-dioxide **219** reacts with triphenyl phosphine affording the zwitterionic salt **220** which, on thermolysis in decalin, gives rise to naphtho[*cd*]dithiol *S,S*-dioxide **18** (81JOC4894). The latter can be obtained also on treating peri-sulfoxydissulfide **222** with phosphorus pentachloride (74ZOB2791). Acidification of a solution of 1,8-disulfinate **223** to pH 1, results in heteroring-closure to naphtho[*cd*]dithiol 1,1,2-trioxide **224** (77JOC3265).



phorus pentachloride (74ZOB2791). Acidification of a solution of 1,8-disulfinate **223** to pH 1, results in heteroring-closure to naphtho[*cd*]dithiol 1,1,2-trioxide **224** (77JOC3265).

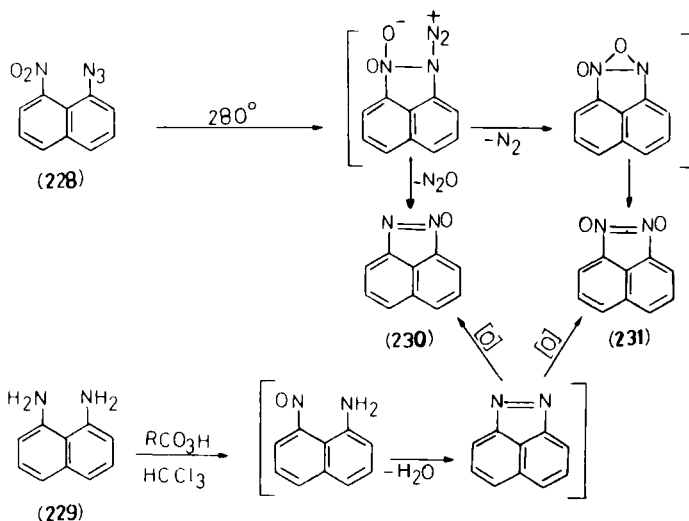


b. *Benzo[cd]indazoles and 1,2-Dihydrobenzo[cd]indazoles*. Benzo[*cd*]indazole **227** possesses a very high reactivity and easily undergoes various conversions under conditions of its formation. Therefore, all attempts at preparative isolation of this compound failed [70JCS(C)

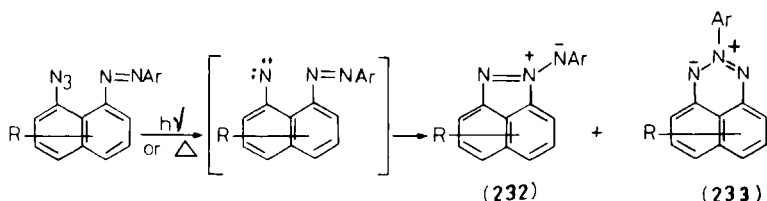


1693; 72JCS(P1)68, 72JCS(P1)72]. However, the simplest representative of this series **227** was obtained in a matrix at low temperature ( $-200^{\circ}\text{C}$ ) by photolysis of 1,8-diazidonaphthalene **225** (76CL823; 82CC86) or 2-methylnaphtho[*de*]triazine **216** (87AG814).

*N*-Oxides **230** and **231** are stable benzo[*cd*]indazole derivatives. A mixture of these compounds was obtained on pyrolysis of 1-azido-8-nitronaphthalene **228** or on oxidation of 1,8-naphthalenediamine **229**. It

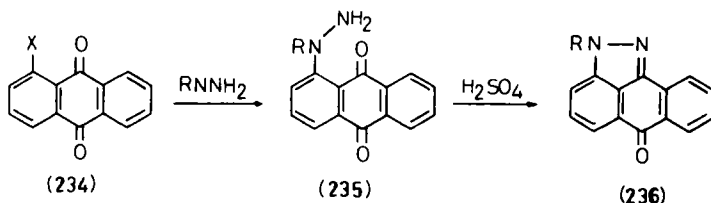


was separated by chromatography [70JCS(C)1693]. On photolysis or thermolysis of 8-azido-1-arylazonaphthalenes, *N*-aryliminobenzo[*cd*]indazoles **232** are formed along with naphtho[*de*]triazine derivatives **233** (78JOC2508; 82JOC1996).

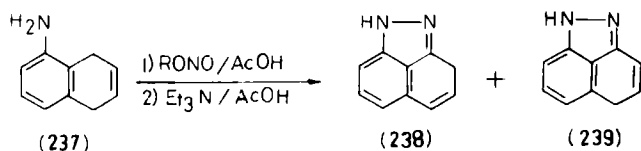


Benzologs of benzo[*cd*]indazole-5-ones **236** (so-called pyrazoloanthrones) are obtained on cyclization of 1-hydrazinoanthraquinones **235**. The latter compounds were synthesized on reduction of 1-anthraquinonyl diazonium salts **234** ( $\text{X} = \text{N}_2^+$ ) or on nucleophilic substitution of the X group in compounds **234** ( $\text{X} = \text{Cl}, \text{SO}_3\text{R}$ ) (60T107; 67GEP1257149; 76ZVK292; 83M11; 84JMC255; 85TL157; 87JMC121). Moreover, with

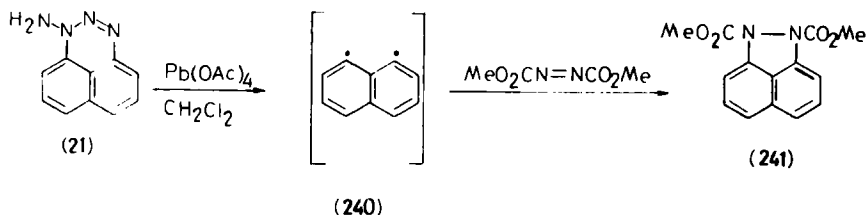
alkyl hydrazines, the reaction center attached to the alkyl group is the most nucleophilic nitrogen atom, and this results in 1-alkylpyrazoloanthrones **236** ( $R' = \text{Alk}$ ).



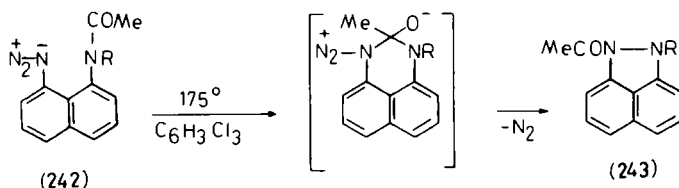
The first information (37JGU739; 67CB2164) about the synthesis of 1,2-dihydrobenzo[*cd*]indazole by reduction of 1,8-dinitronaphthalene or naphtho[*de*]-2,1,3-thiadiazine was incorrect [72JCS(P1)68]. It was later shown that in solution, 1,2-dihydrobenzo[*cd*]indazole is in equilibrium with 1,3- and 1,5-dihydrobenzo[*cd*]indazoles **238** and **239**. The mixture of the latter compounds was obtained on diazotization of 1-amino-5,8-dihydronaphthalene **237**, and it was separated by chromatography [72JCS(P1)68].



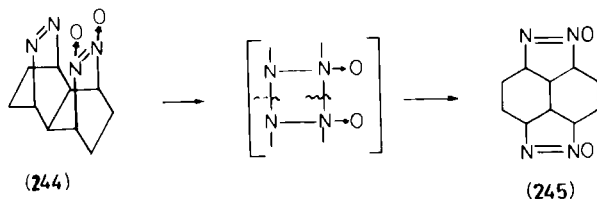
The mixture of isomers **238** and **239** is also obtained as the result of saponification and decarboxylation of 1,2-dicarbomethoxy-1,2-dihydrobenzo[*cd*]indazole **241** or on reduction of benzo[*cd*]indazole *N*-oxides **230** and **231** [70JCS(C)1693; 72JCS(P1)68] and *N*-arylimines **233** (78JOC2508). The cycloaddition of dimethyl azodicarboxylate to dehydronaphthalene **240**, which was generated on oxidation of 1-aminonaphtho[*de*]triazine **21** by lead tetraacetate, leads to 1,2-dicarbomethoxy-1,2-dihydrobenzo[*cd*]indazole **241** [69JCS(C)760].



Representatives of 1,2-dihydrobenzo[*cd*]indazole **243** with the same or different substituents at the nitrogen atoms are formed on pyrolysis

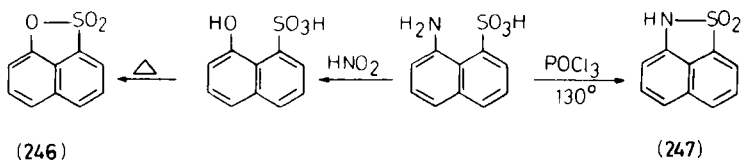


of *N,N*-disubstituted 1-amino-8-azidonaphthalene derivatives **242** [72-JCS(P1)72]. A very unusual photochemical conversion of bis-diazodecalin *N,N*-dioxide **244** leads to the decahydroderivative of bis-benzo[*cd*]indazole **245** (82TL1251).

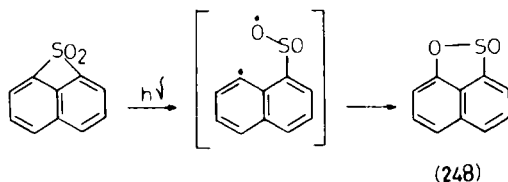


## 2. Heterocycles with Different Heteroatoms

Heterocycles are known to have  $\text{O}-\text{S}$ ,  $\text{S}-\text{N}$ , and  $\text{O}-\text{N}$  bonds. The cyclization of peri-hydroxy and peri-amino-substituted naphthalene sulfonic acids gives rise to 1,8-naphthosultone **246** and 1,8-naphthosultam **247**, respectively (33MI2; 63MI1). On gas phase photolysis of naphtho[*bc*]-

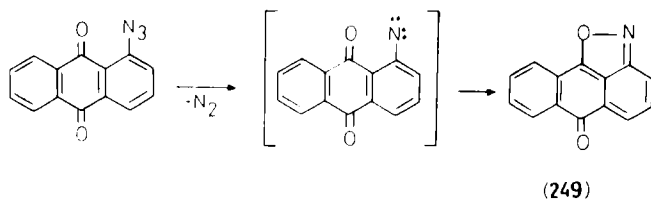


thiethe *S,S*-dioxide, naphtho[*cd*]oxathiol *S*-oxide **248** was found among the other products (67LA96).

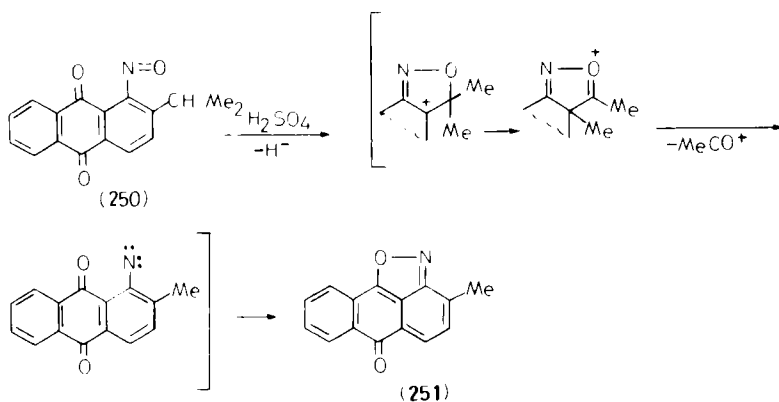


Formation of an  $\text{N}-\text{O}$  bond, together with the isooxazole ring closure, proceeds on thermal decomposition of 1-azidoanthraquinones and leads to

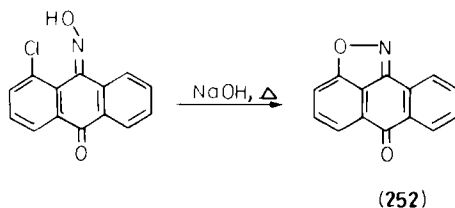
isooxazoleanthrones **249** (83MI1; 84ZOR2452). The unusual transfor-



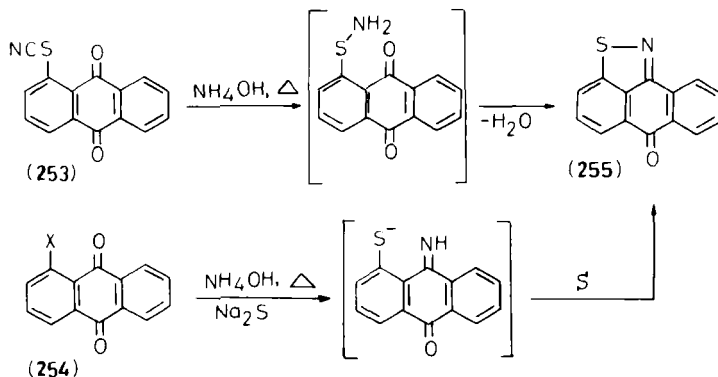
mation of 1-nitroso-2-isopropylantraquinone **250** under strongly acidic conditions gives rise to isooxazoleanthrone **251** (68DOK1099). Isooxa-



zoleanthrone **252**, having another orientation of the heteroatom group, is formed as the result of base-catalyzed cyclization of 1-chloroanthraquinone oxime (57JCS1900).



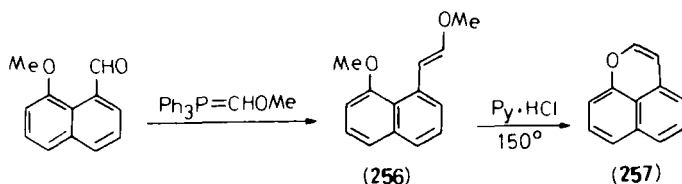
Isothiazoloanthrone **255** is formed on heating 1-thiocyanoanthraquinone **253** with ammonia or on reacting 1-chloro and 1-sulfoanthraquinones **254** (X = Cl, SO<sub>3</sub>H) with ammonia, sodium sulfide, and sulfur [76-IJC(B)625; 79HOU414; 83MI1].



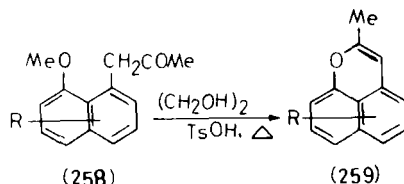
## D. PERI-HETEROCYCLES WITH A SIX-MEMBERED HETERORING HAVING A SINGLE HETEROATOM

### 1. Naphtho[bc]annelated Heterocycles

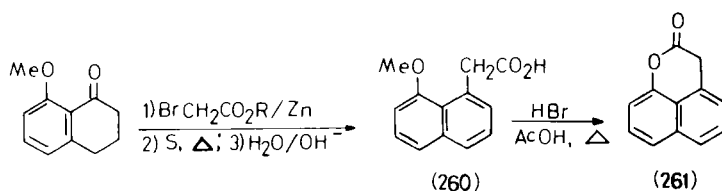
a. *Naphtho[bc]pyrans*. The simplest naphtho[bc]pyran **257** is formed on heating pyridine hydrochloride with enol ether **256** obtained from peri-



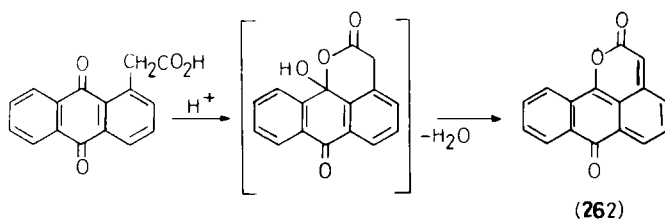
methoxynaphthaldehyde and methoxymethylenephosphoran (73TL843; 75S796). Peri-methoxy-substituted  $\alpha$ -naphthylacetone derivatives **258** are converted into 2-methylnaphtho[bc]pyrans **259** on heating with toluene sulfonic acid in ethylene glycol (83LA844).



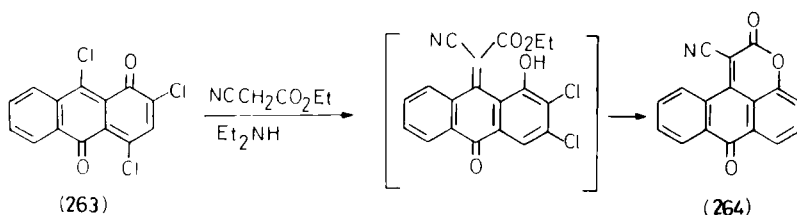
The analogous principle of heterocyclization was used in the synthesis of naphtho[bc]pyran-2-one **261** from peri-methoxynaphthylacetic acid **260**, which was obtained from 8-methoxytetralone (76JA4276). Pyronoan-



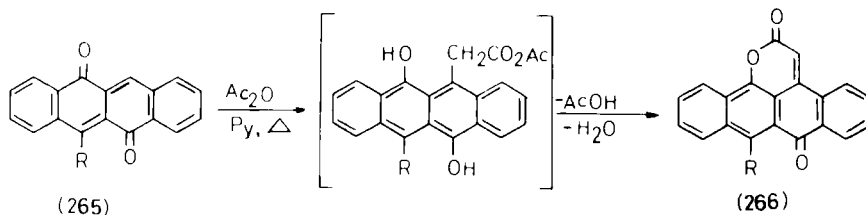
throne **262**, which has a 1,10-anthraquinonoid structure, is formed from anthraquinonyl-1-acetic acid on acidic catalysis (76ZOR2041; 78ZOR1535). The interaction between the chlorinated 1,10-anthraquinone



**263** and cyanoacetic ester in the presence of triethylamine gives rise to pyronoanthrone **264** having a 9,10-anthraquinonoid structure (79ZOR-1033).

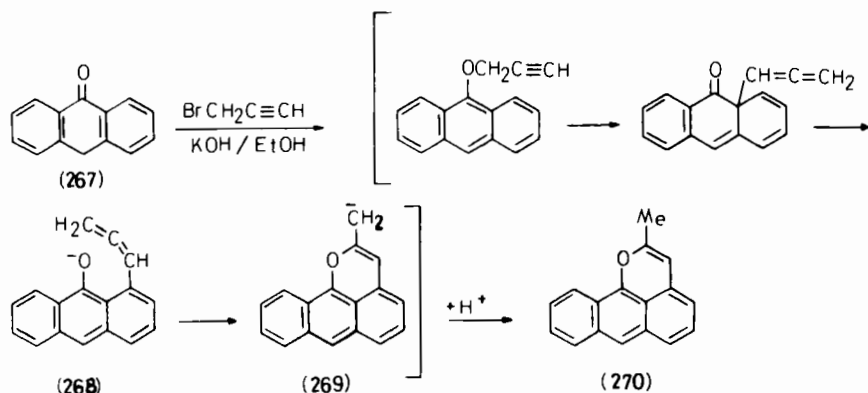


The interesting conversion resulting in pyronoanthrone benzolog **266** occurs on boiling 5,11-naphthocenoquinones **265** in acetic anhydride in the presence of pyridine (80ZOR1933; 85ZOR453). An unusual reaction lead-

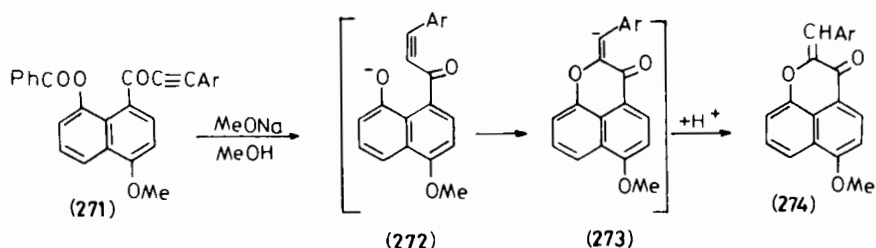


ing to 2-methylbenzo[*c*]naphtho[*bc*]pyran **270** takes place between anthrone and allyl bromide in an alkaline medium [86IJC(B)1024]. An analo-

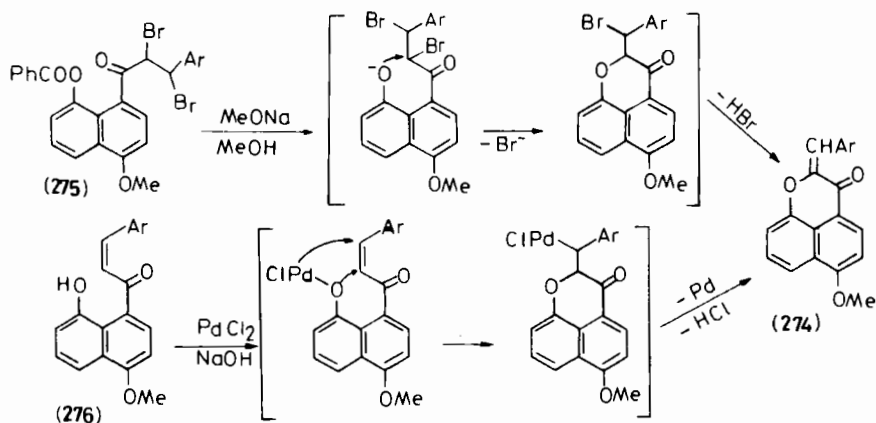




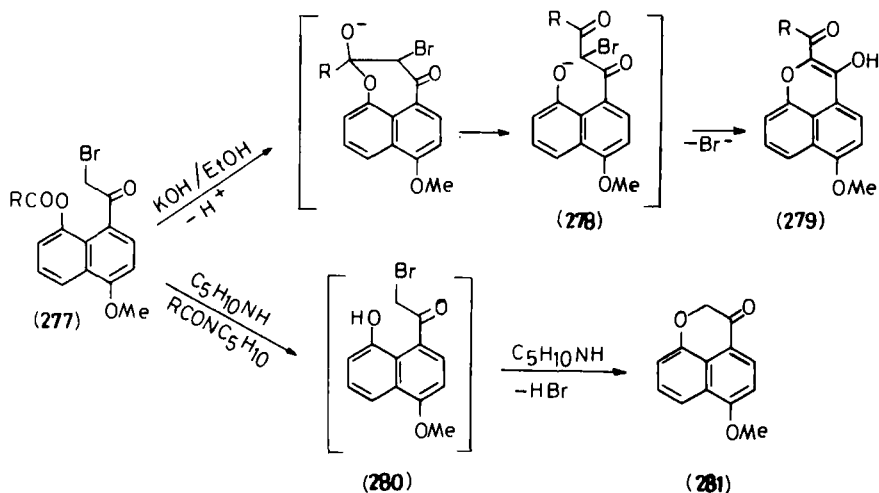
gous course of reaction (268  $\rightarrow$  269) involves the intramolecular attack on the carbon atom of a multiple bond by the phenolate anion which results in pyran ring-closure (272  $\rightarrow$  273) in the case of peri-benzoyloxynaphthylarylethynyl ketones **271** and sodium methylate (81ZOR2002). The final product of this reaction is 2-arylmethylidenenaphtho[bc]pyran-3-ones **274**.



Compounds **274** have also been obtained in reactions of peri-benzoyloxydibromochalcones **275** with sodium methylate or peri-hydroxychalcones **276** with palladium chloride and sodium hydroxide.

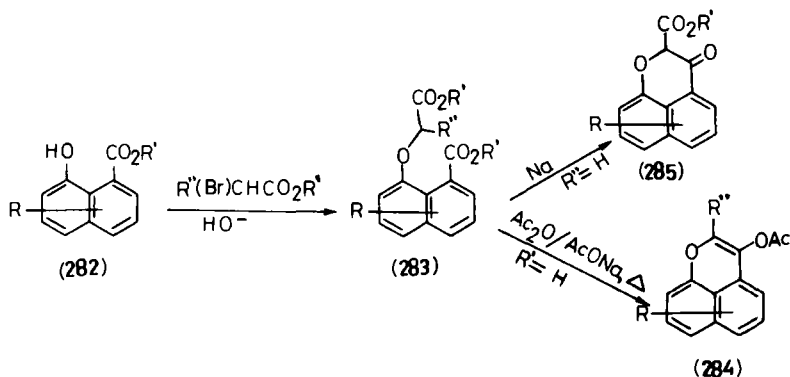


cones **276** with palladium chloride in the presence of a base (81ZOR2002). By the action of strong bases (KOH, NaOMe), peri-acyloxynaphthyl- $\alpha$ -bromomethyl ketones **277** undergo rearrangement to 2-acyl-3-hydroxy-6-methoxynaphtho[*bc*]pyrans **279**, whereas on treating the former compounds with piperidine, deacylation is the primary step (**277**  $\rightarrow$  **280**), followed by cyclization into 6-methoxy-naphtho[*bc*]pyran-3-one **281** (89TH1).



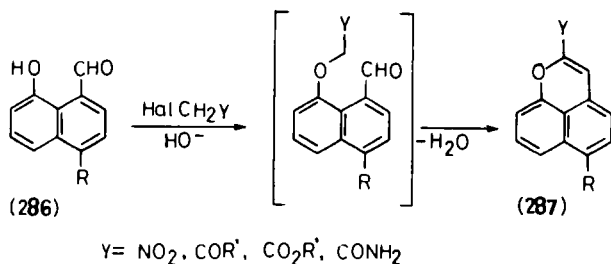
The interaction of peri-acyloxybromo ketones **277** with aromatic aldehydes in the presence of sodium methylate gives rise to 2-arylmethylene derivatives of naphtho[*bc*]pyran-3-one **274** (89TH1). In all reactions just described, the pyran ring-closure occurs by formation of a C—O bond between the  $\beta$ -carbon atom of a substituent in position 1 of the naphthalene nucleus and the oxygen atom of an 8-hydroxy group.

In another approach, the construction of a pyran ring is carried out by

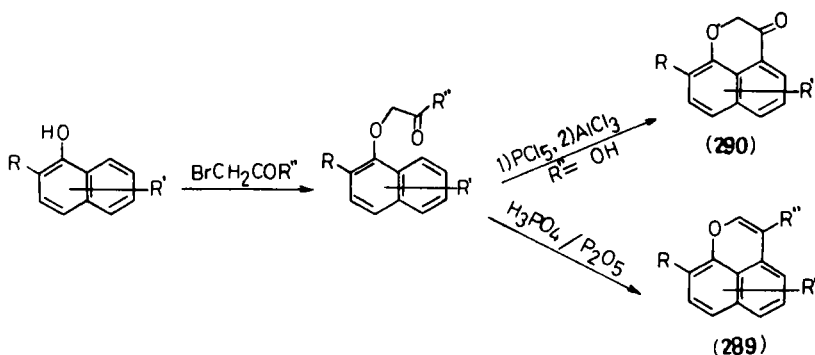


the formation of a C—C bond between the carbon atoms of a carbonyl and the activated *O*-alkyl groups situated in positions 1 and 8 of the naphthalene nucleus. The dicarboxylic acid derivatives **283**, obtained on carboxy and carboalkoxy alkylation of 1,8-hydroxynaphthoic acid and esters **282**, are converted into 2-substituted 3-acetoxynaphtho[*bc*]pyrans **284** [63JCS2907; 66JCS(C)523] or naphtho[*bc*]pyran-3-ones **285** [67JCS(C)1782] under Dieckmann condensation conditions.

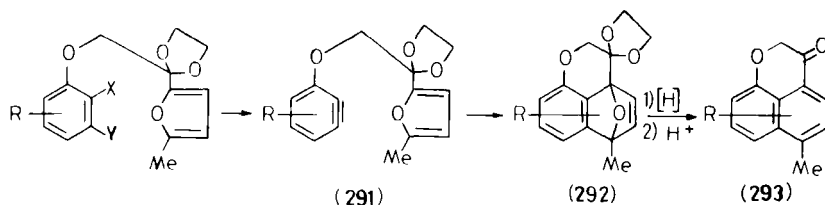
An idea similar to the previous reaction was applied to the synthesis of 2-functional-substituted naphtho[*bc*]pyrans **287** from peri-hydroxynaphthaldehydes **286** and  $\alpha$ -halogenomethylene-active com-



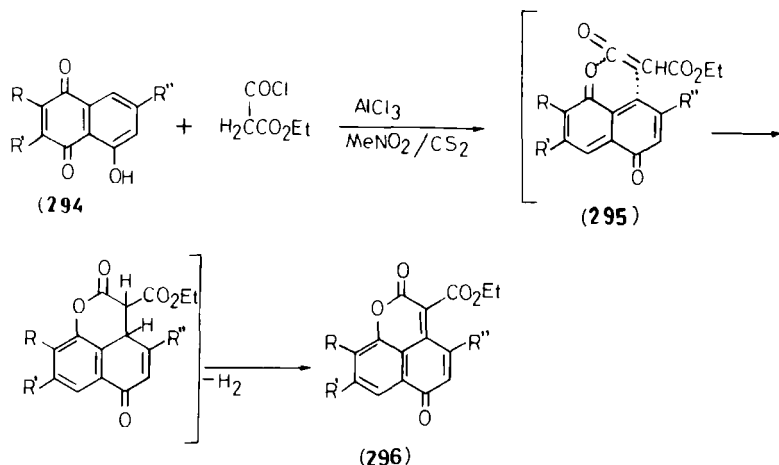
pounds in the presence of bases (88JHC539). One more variant of the attachment of a pyran ring includes *O*-oxomethylation and *O*-carboxymethylation of 2-substituted 1-naphthols followed by intramolecular *C*-alkylation or *C*-acylation to give naphtho[*bc*]pyrans **289** and naphtho[*bc*]pyran-3-ones **290** (63HCA415, 63JCS2907; 67M11).



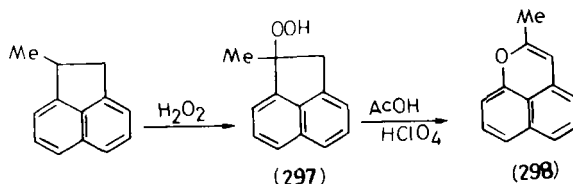
Some non-standard synthetic pathways to compounds of the naphtho[*bc*]pyran series are known. One consists in generation of the complex heterocyclic dehydrobenzene derivative **291**, which then undergoes an intramolecular [4 + 2] cycloaddition to afford the bridge system **292**. The latter is transformed into naphtho[*bc*]pyran-3-one **293** on reduction, followed by treatment with acid (81TL4877; 86AJC635). An unusual course



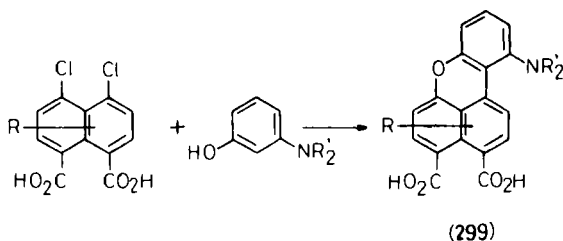
employs the reaction of juglone and its derivatives **294** with  $\alpha$ -chloroformylacetic ester and aluminum chloride, resulting in naphtho[*bc*]pyran-2,6-diones **296** [84JCS(P1)1957]. The mechanism of this conversion was not discussed in the original paper. From our point of view, the formation of **296** may be explained by [4 + 2] cycloaddition of the quinonoid juglone tautomer **295** to carboethoxy ketene. The latter is formed as the result of eliminating hydrogen chloride from  $\alpha$ -chloroformylacetate.



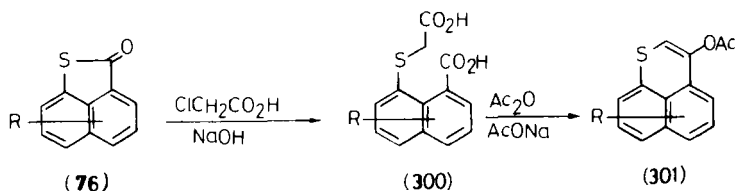
Oxidation of methylacenaphthene by hydrogen peroxide gives rise to hydroperoxide derivative **297**, which is converted into 2-methylnaphtho[*bc*]pyran **298** on treatment with acetic acid containing cat-



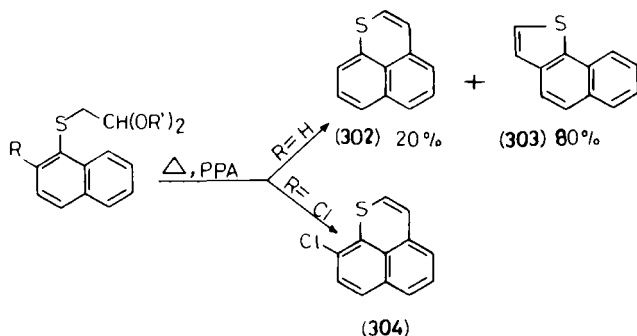
alytic amounts of perchloric acid (63JCS2907). The interaction between 1,8-dichloro-4,5-dicarboxynaphthalenes and *m*-dialkylaminophenols leads to polysubstituted benzologs of naphtho[*bc*]pyran **299** (76JAP76-14930).



b. *Naphtho[bc]thiapyrans*. The principles of heterocyclic construction of naphtho[bc]thiapyrans are the same as those for naphtho[bc]pyrans. The general pathway to 3-acetoxy derivatives of naphtho[bc]thiapyran **301** consists of the synthesis of peri-carboxynaphthothia-acetic acids **300** from naphthothialactones **76**. The acids **300** are then cyclized into desired compounds **301** in acetic anhydride with sodium acetate [12-

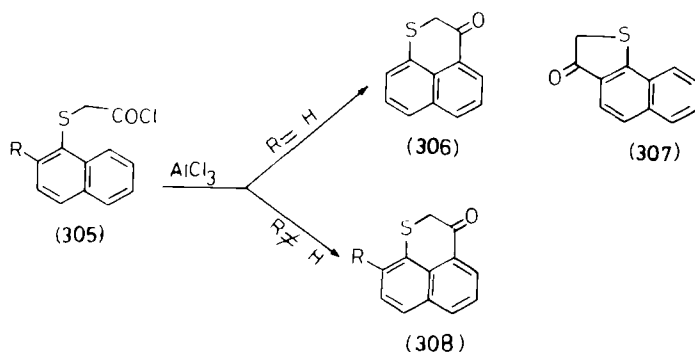


LA(388)1; 68M2VK462; 70KGS1031; 73KGS1034). The simplest naphtho[bc]thiapyran **302**, along with naphtho[*b*]thiophene **303** which is a product of ortho-cyclization, is formed on heating  $\alpha$ -naphthothiaacetic aldehyde acetal in polyphosphoric acid [51PIA(A)71; 57CI(L)464; 73JCS(P1)2956].

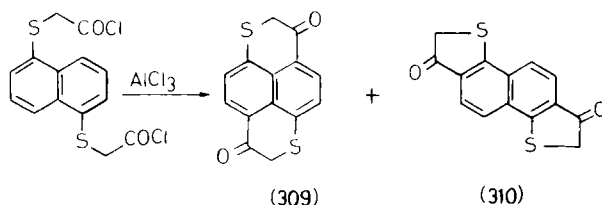


If the position ortho to the sulfur atom is blocked by a substituent, then only attack on the peri-position takes place. For instance, 2-chloro-1-naphthothiaacetic aldehyde acetal gives rise to 9-chloronaphtho[bc]thiapyran **304** [51PIA(A)78]. By analogy, the heterocyclization of  $\alpha$ -naphthothiaacetic acid chloride **305** ( $R = H$ ) leads to a mixture of peri- and

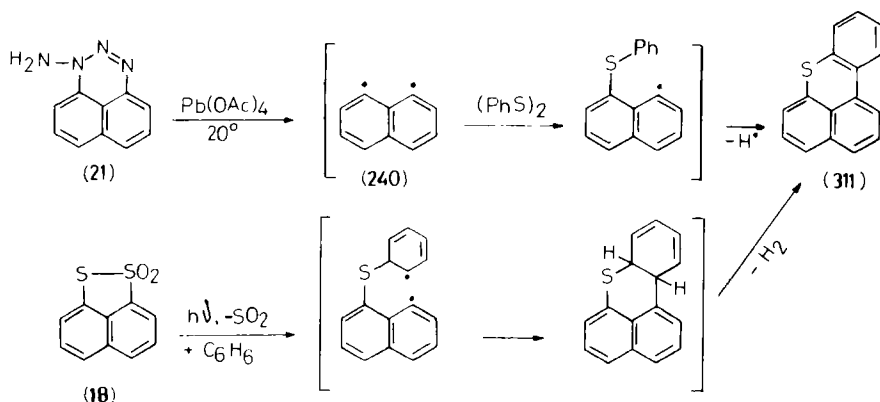
ortho-annelated isomers **306** and **307** (58VRP110951; 59UKZ206), whereas 2-substituted derivatives of acid **305** ( $R \neq H$ ) give rise only to naphtho[*bc*]thiapyran-3-ones **308** (49G50; 8JOC4060).



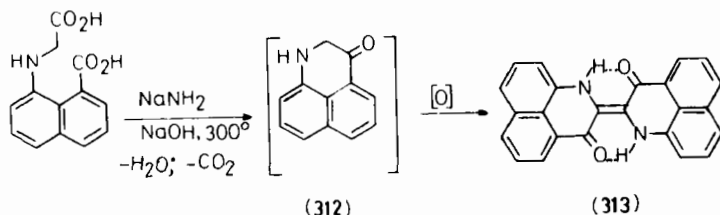
Under conditions of the Friedel-Crafts reaction, 1,5-naphthalene-bis-thioglycolic acid chloride forms a mixture of peri- and ortho-annelated isomers **309** and **310**, with major predominance of the latter (49G286;



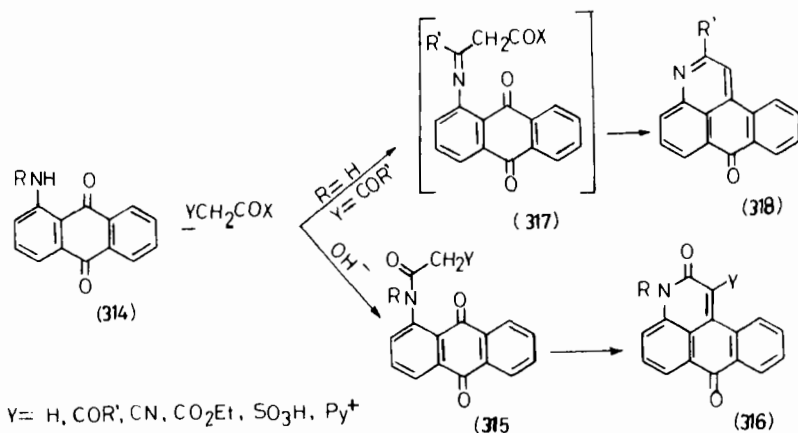
64JOC2372). The interaction of 1,8-dehydronaphthalene **240**, generated from *N*-aminonaphtho[*de*]triazine **21**, with diphenyldisulfide (83TL821) or photolysis of naphtho[*cd*]dithiol *S,S*-dioxide **18** [77CI(L)661] results in low yields of benzo[*e*]naphtho[*bc*]thiapyran **311**, which also is obtained in other mixtures.



c. *Naphtho[bc]pyridines*. In Sections II,D,1,a and b, principles of heteroring attachment to the naphthalene nucleus using the Dieckmann reaction and other similar intramolecular condensations of dicarbonylnaphthalene derivatives are applied to the synthesis of 1*H*-naphtho[bc]pyridines. Under conditions of the indigo synthesis, the cyclization of 1-carboxy-8-naphthylaminoacetic acid to 1,2-dihydronaphtho[bc]pyridine-3-one **312** is accompanied by oxidative dimerization of the latter compound, resulting in a peri-annulated dye of the indigo type **313** (23JCS224). In the anthraquinone series, interactions



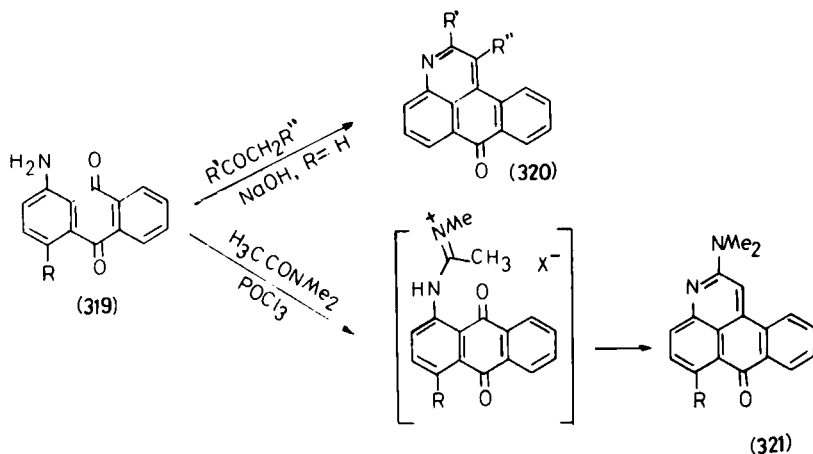
of 1-aminoanthraquinones **314** ( $R = H, \text{Alk}, \text{Ar}$ ) with carbonyl reagents have been used to prepare so-called anthrapyridones **316** and **318** [55GEP930042; 61CB3119; 72KGS1651; 74KGS679, 74ZOR838; 76ZOR177, 76ZOR1106; 77IJC(B)895; 80ZOR160, 80ZOR230; 83MI1].



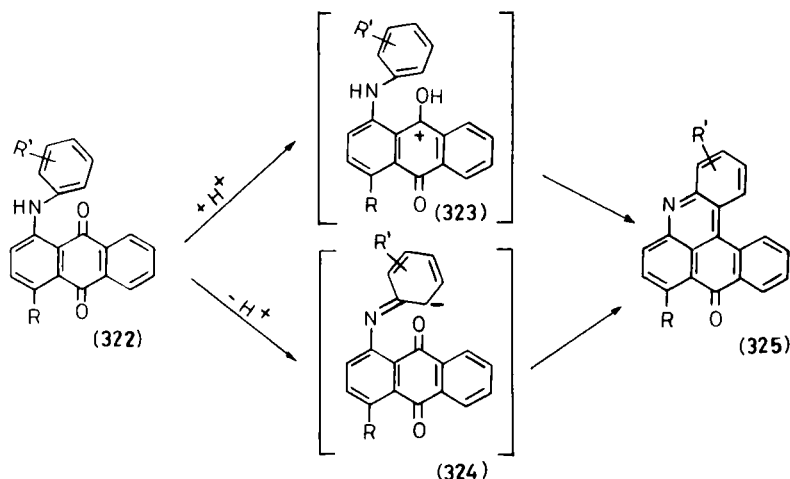
In those cases when the carbonyl reagent  $\text{YCH}_2\text{COX}$  contains a second carbonyl group ( $Y = \text{COR}'$ ), the character of the final products **316** or **318** depends on the course of reaction towards the amino group; this is determined by the nature of catalysis. Thus, on basic catalysis, *N*-acylation occurs (**314**  $\rightarrow$  **315**), whereas in acidic medium, azomethine **317** is obtained. The latter compound was not isolated since the conditions of its

formation favor cyclization to pyridinoanthrone **318**. *N*-Acylated products **315** may be isolated, but as a rule, *N*-acylation and heterocyclization combine to give the final product **316**.

For the carbonyl component in reactions with 1-aminoanthraquinones **319**, one can use methyl and methylene ketones as well as adducts between *N,N*-dimethylacetamide and phosphorus oxychloride, which leads to py-

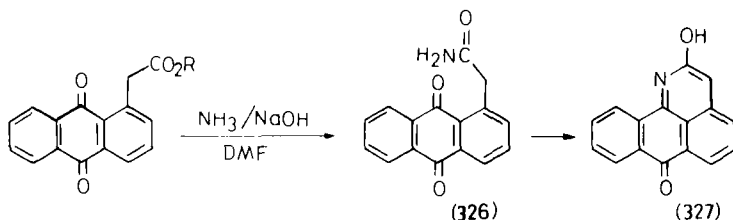


ridinoanthrones **320** and **321** (61CB3119; 76ZOR177; 83M11). A place for intramolecular electrophilic attack may be the 2'-position of an *N*-aryl substituent in 1-arylaminoanthraquinones **322**. In this case, the reaction results in benzo derivatives of pyridinoanthrones **325**, which are called keramidonines [65VRP176021; 71CCC2005; 76IJC(B)213; 81ZOR26<sub>1</sub><sup>3</sup>].



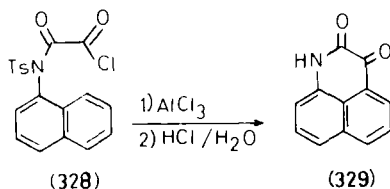


Usually the reaction is carried out in sulfuric acid, and obviously it proceeds via the oxonium intermediate **323**. In this case, the rate of formation of keramidonines **325** strongly depends on the position and nature of a  $R'$  substituent in the  $N$ -aryl nucleus (71CCC2005). For those cases when  $R$ , in position 4 of anthraquinone **322**, is a strong electron-acceptor, basic catalysis is possible, and the anionic intermediate **324** is a precursor of keramidonine **325** (81ZOR2631). Pyridinoanthrones **327** with the other heterocyclic orientation are formed as a result of cyclization of 1-anthraquinoylacetic acid amide **326** (72G697; 75GEP2434466; 76VRP532600; 81ZOR803; 81ZOR2631).

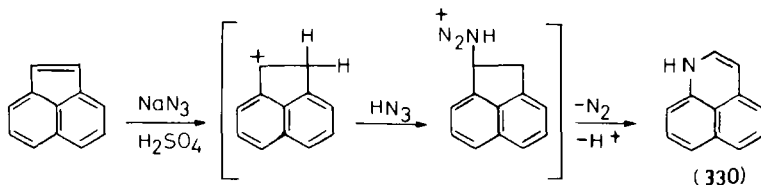


The described reactions of anthraquinones leading to benzologs of 1*H*-naphtho[*bc*]pyridine, obviously, should take place also in the 1,4-naphthoquinone series. However, no information about such transformations has been published yet.

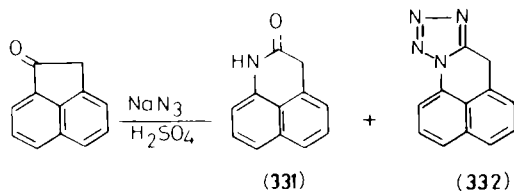
Construction of a nitrogen six-membered heteroring may be achieved by intramolecular  $C$ -acylation. This pathway was used, for instance, in the synthesis of 1*H*-naphtho[*bc*]pyridine-2,3-dione **329** from  $N$ -tosyl- $N$ -( $\alpha$ -naphthyl)aminooxallyl chloride **328** (28USP1698894). Approaches to 1*H*-



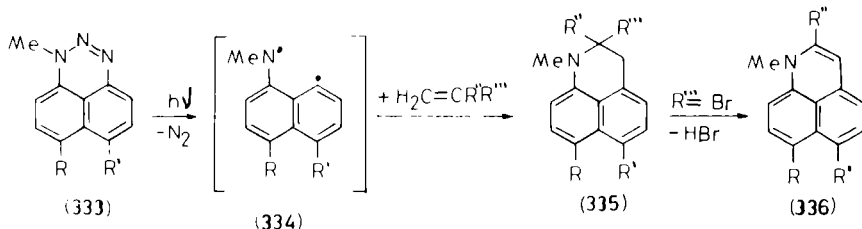
naphtho[*bc*]pyridines, including transformations of a five-membered carbocycle into a six-membered nitrogen heterocycle, have been described. Thus, following easy oxidation by air, the simplest 1*H*-naphtho[*bc*]pyridine **330** was obtained in low yield from acenaphthylene and hydrazoic acid (63JCS2907).



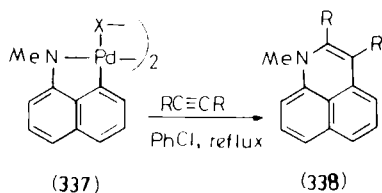
In a similar reaction, acenaphthenone gives a complex mixture from which 1,3-dihydronaphtho[*bc*]pyridine-2-one **331** and derivative **332** are extracted by chromatography (63JCS2907). Construction of the 1*H*-naphtho[*bc*]-pyridine nucleus is based on generation of biradical derivatives of  $\alpha$ -naphthylamine, followed by interaction with compounds having multiple carbon-carbon bonds.



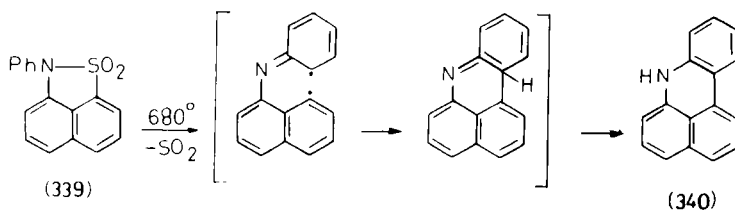
The biradical intermediate **334**, obtained on photolysis of compounds **333**, reacts with alkenes or bromoethylene to afford 1*H*-naphtho[*bc*]-pyridine (*R*, *R* = *H*) or 1*H*-acenaphthylene[4,5-*bc*]pyridine (*R*, *R* = *HC=CH*) derivatives **335** and **336** (69JA1035; 70JCS(C)298). Prob-



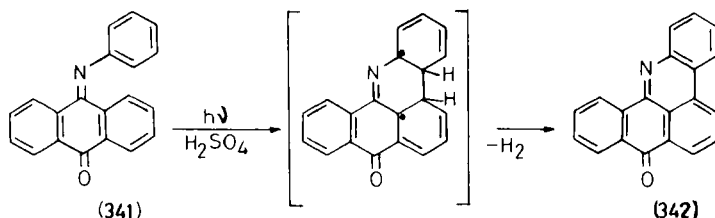
bly, the biradical mechanism takes place also in reaction of a palladium derivative of *N*-methyl- $\alpha$ -naphthylamine **337** with acetylenes, which leads to tri-substituted 1*H*-naphtho[*bc*]-pyridines **338** (*R* = *CF*<sub>3</sub>, *Ph*, *CO*<sub>2</sub>*Me*) (87CC565).



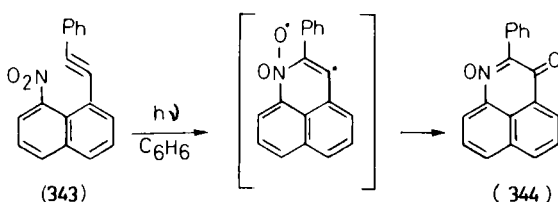
Pyrolysis of *N*-phenylnaphthosultone **339** gives rise to 1*H*-benzo[*e*]naphtho[*bc*]pyridine **340** (72JOC2152). The photochemical het-



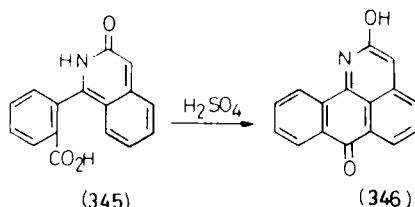
erocyclization of *N*-phenyliminoanthraquinone **341** leads to benzo[*b*]-pyridinoanthrone **342** (70TL2835). The unusual cyclization resulting in



2-phenylnaphtho[*bc*]pyridine-3-one *N*-oxide **344** is observed on irradiation of peri-nitrophenylethynynaphthalene **343** (71CJC3596).

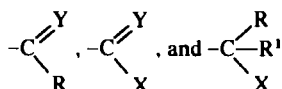


Attachment of a carbocyclic fragment to an isoquinoline was achieved in the synthesis of 2-hydroxypyridinoanthrone **346** by intramolecular C-acylation of 1-(2'-carboxy)phenylisoquinolone **345** in sulfuric acid (75GEP2501742; 79HOV414).



## 2. Naphtho[*cd*]annelated Heterocycles<sup>3</sup>

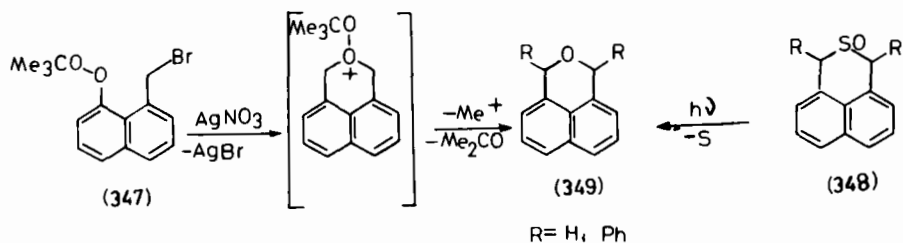
a. *Naphtho[cd]pyrans*. The general principle of construction of a naphtho[*cd*]pyran nucleus employs the heterocyclization of naphthalene derivatives having, in positions 1 and 8, the same or different groups



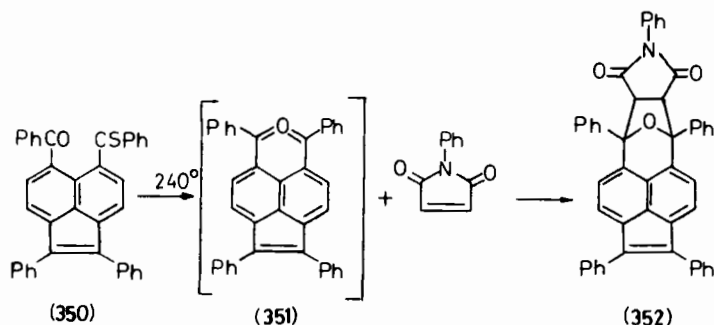
or substituents that can be easily transformed to such groups under heterocyclization conditions.

<sup>3</sup> Part of the data discussed in this paragraph has been taken from the monograph by M. M. Dashevskii (66MI1). We refer to it instead of the original sources given in that monograph.

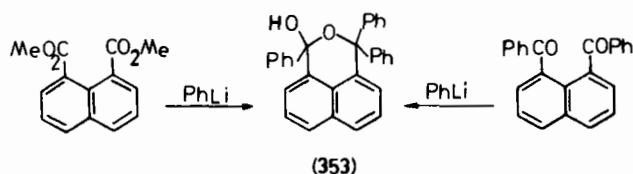
Naphtho[*cd*]pyran derivatives with various oxidation states of the  $\alpha, \alpha'$ -carbon atoms in the heteroring have been described. 2,9-Dihydronaphtho[*cd*]pyran derivatives **349** are formed on treating peribromomethylperoxide **347** with silver nitrate (84TL3769; 86JOC2612) or on photolysis of naphtho[*cd*]thiapyran *S*-oxide **348** (73TL3605).



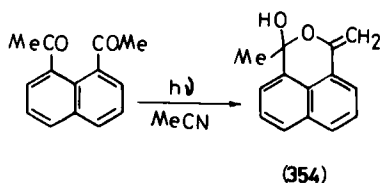
Compounds **352**, having the same oxidation state of the  $\alpha, \alpha'$ -carbon atoms in the pyran ring as in compound **349**, are obtained on heating thio ketone **350** with *N*-phenylmaleinimide. It was assumed that this reaction proceeds via formation of the intermediate **351**, which has the nonclassical tetravalent oxygen heteroatom (69JA3953).



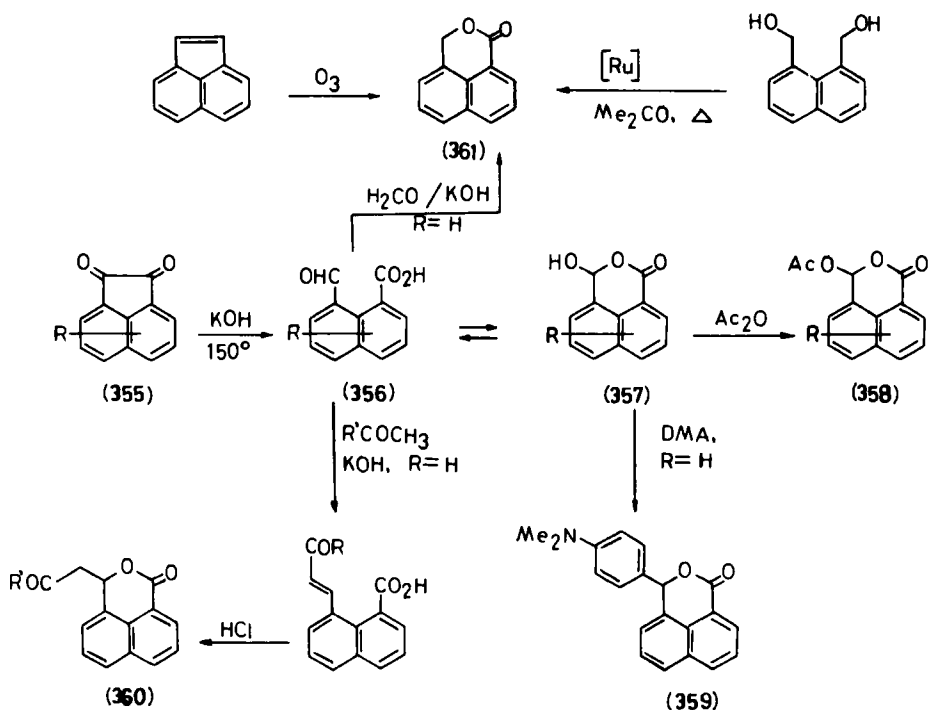
The reaction of phenyl lithium with a dimethylnaphthalic ester or with 1,8-dibenzoylnaphthalene gives rise to 2,2,9-triphenyl-9-hydroxynaphtho[*cd*]pyran **353** (31CB2405). 2-Methylene-9-hydroxy-9-



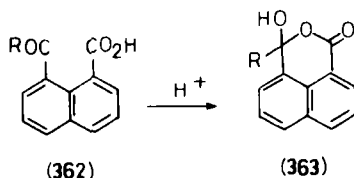
methylnaphtho[*cd*]pyran **354** is obtained on photolysis of 1,8-diacetylnaphthalene (78CC589).



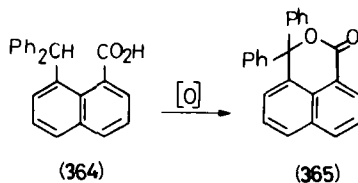
On heating with alkali hydroxides or diethylthiodiglycolate in an alkaline medium, acenaphthenequinones **355** are transformed into 1,8-formylnaphthoic acids **356**, which are in equilibrium with  $\alpha$ -hydroxynaphthalides **357** (66MI1; 73ZOR597, 73ZOR1490). The various naphtho[*cd*]pyran derivatives **358–361** are obtained on interacting aldehyde acid **356** with acetic anhydride, dimethyl aniline (DMA), methyl ketones, or formaldehyde (66MI1). Naphthalide **361** is formed also from 1,8-bis-hydroxymethyl naphthalene in the presence of ruthenic complex (81TL5327) or on ozonolysis of acenaphthylene (66MI1).



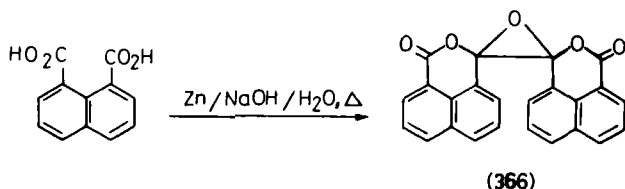
Similarly, with 1,8-aldehyde acid **356** in acidic medium, pericarboxynaphthyl ketones **362** are transformed into  $\alpha$ -hydroxynaphthalides **363** ( $R = \text{Alk, Ar}$ ) [66MIP1; 73JCS(P2)345, 73JCS(P2)1144; 74JCS(P2)358;



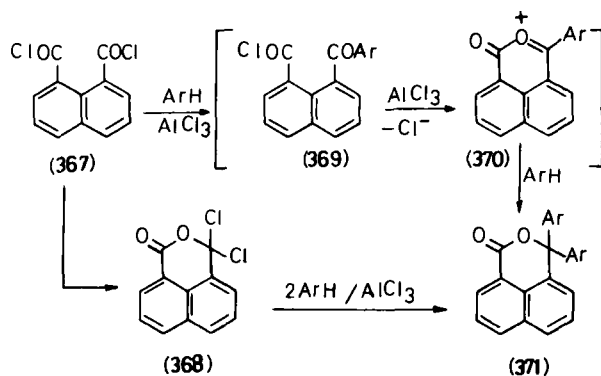
76S249]. Oxidation of 1,8-diphenylmethylnaphthoic acid **364** gives rise to  $\alpha,\alpha$ -diphenylnaphthalide **365** (66M11).

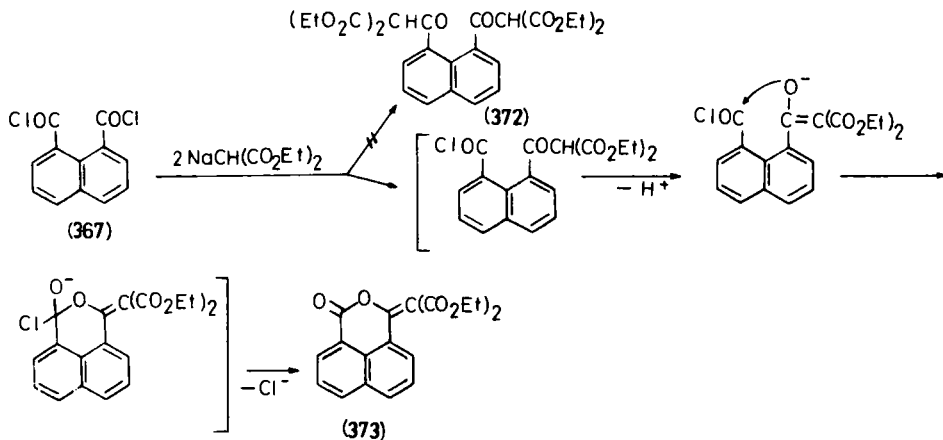


On reaction with zinc dust in alkaline medium, naphthalic acid is subjected to reductive dimerization with so-called deoxynaphthalic anhydride **366** as the result (13CB1484). The formation of diarylnaphthalides **371** on



interaction of naphthaloyl dichloride **367** with electron-donor aromatic compounds in the presence of aluminum chloride is explained by the transformation of acid chloride **367** into dichloronaphthalide **368** (24JCS2116; 66M11). In our view, the mechanism including monoacylation

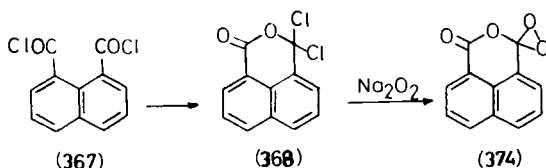




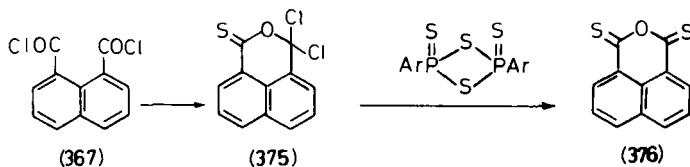
SCHEME 7

(367  $\rightarrow$  369) and heterocyclization (369  $\rightarrow$  370), followed by interaction of the carboxonium intermediate 370 with the second molecule of the aromatic compound is more probable in this case. This proposal is in good agreement with data indicating that tautomerism between acid chloride 367 and dichloronaphthalide 368 has not been found (27JCS1124).

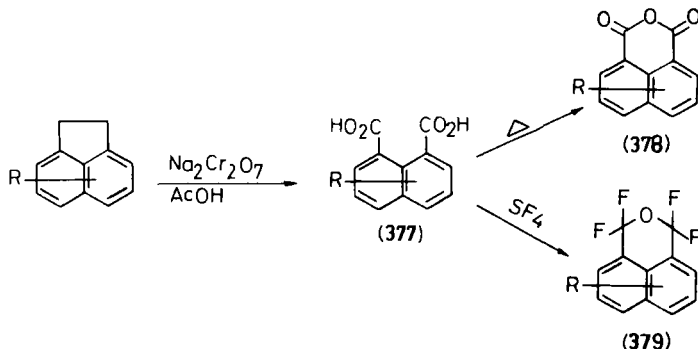
Without postulating the formation of dichloronaphthalide 368, one may explain using Scheme 7 the reaction of naphthaloyl dichloride 367 with two molecules of sodium malonic ester, which does not result in the expected 1,8-dimalonylnaphthyl diketone 372, but leads to a 2-malonylydene derivative of naphtho[cd]pyran-9-one 373 (36MI3). However, we do not insist on the suggested mechanisms for the reactions of naphthaloyldichloride 367 with aromatic compounds or sodium malonic ester; one can assume the alternative course via dichloronaphthalide 368. Moreover, hemo-



luminescence has been detected on interaction of naphthaloyldichloride 367 with sodium peroxide. This fact is connected with the formation of dichloronaphthalide 368, followed by its transformation into the corresponding heterocyclic peroxide 374 [85JCR(S)140]. Moreover, the formation of the thione analog of dichloronaphthalide 375 from naphthaloyldichloride 367, followed by the transformation of 375 to dithione 376 has been reported (63CCC1292; 84JA6084).



The most common compounds from the naphtho[cd]pyran series are naphthalic anhydride and its various derivatives **378** substituted in the naphthalene nucleus. These derivatives are formed on heating naphthalic acids **377**, which are obtained on oxidation of the corresponding acenaphthenes. The syntheses of naphthalic acids **377** and their anhydrides are described in a monograph (66M11). The interaction between naphthalic acid and sulfur tetrafluoride leads to 2,2,9,9-tetrafluoronaphtho[cd]pyran **379** (73ZOR689).

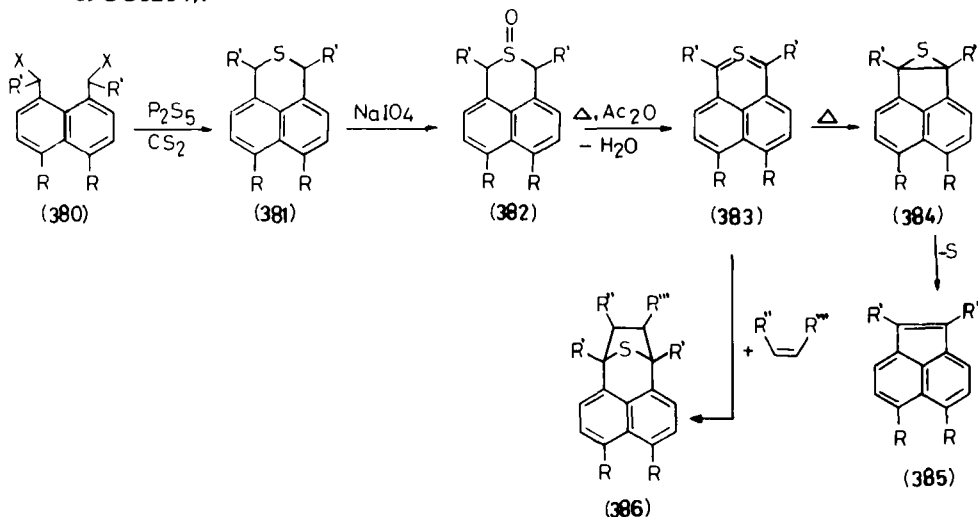


b. *Naphtho[cd]thiapyrans*.  $\alpha,\alpha'$ -Dehydro derivatives **383** with a tetravalent sulfur atom are the most interesting representatives of the naphtho[cd]thiapyran class. Compounds having such a structure are similar with dehydrobenzene in reactivity, and therefore, it is impossible to isolate them. However, they can be generated in solution and thus can be used in the further conversions. The reactivity of  $\alpha,\alpha'$ -dehydronaphtho[cd]thiapyrans decreases significantly in acenaphthylene (**383c,d**), and especially in 2,5,6,9-tetra-substituted acenaphthylene derivatives **390**. This is obviously determined by the  $14\pi$ -electron perimeter and the stabilizing influence of substituents (Br, Ph). Such acenaphthylene derivatives are stable, and they exist in solution (**383c**,  $\text{R}' = \text{H}$ ) or crystalline state (**383d**,  $\text{R}' = \text{Ph}$ ; **390**).

One of the pathways to synthesis of  $\alpha,\alpha'$ -dehydronaphtho[cd]thiapyrans **383a-d** includes step-by-step heterocyclization of peri-bis-bromomethyl, peri-bis-hydroxymethyl, or peri-bis-hydroxybenzyl-



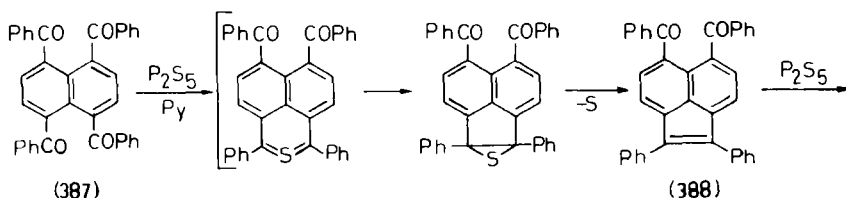
substituted naphthalene, acenaphthene, acenaphthylene, or 1,2-dibromoacenaphthylene derivatives **380** ( $X = \text{Br}, \text{OH}$ ;  $R' = \text{H}, \text{Ph}$ ) into the corresponding naphtho [*cd*]thiapyrans **381**. This is followed by oxidation to *S*-oxides **382** and dehydration of the latter compounds (65T3073; 67JA3640, 67JA3641, 67TL4057; 68JA1676, 68JA4190; 69CC1214):

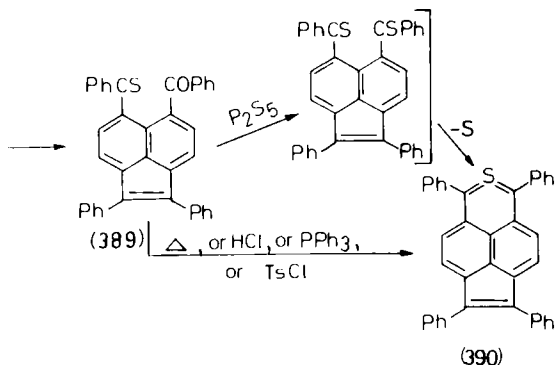


$R$  (a):  $\text{H}, \text{H}$ ; (b):  $\text{H}_2\text{C}=\text{CH}_2$ ; (c):  $\text{HC}=\text{CH}$ ; (d):  $\text{BrC}=\text{CBr}$

Compound **383c** ( $R' = \text{H}$ ) was also obtained on treatment of naphtho [*cd*]thiapyran **381c** ( $R' = \text{H}$ ) with phenylmagnesium bromide in the absence of light and oxygen (69CC1214). Under such conditions, the solution of this compound is rather stable, which allows the  $^1\text{H}$ -NMR spectrum to be recorded. Unstable  $\alpha, \alpha'$ -dehydronaphtho [*cd*]thiapyrans **383a, b** are generated in the presence of a dienophile in order to obtain adducts **386**. In the absence of a dienophile, the thermal valence isomerization occurs; this leads to thiiranes **384** and then to acenaphthylenes **385**.

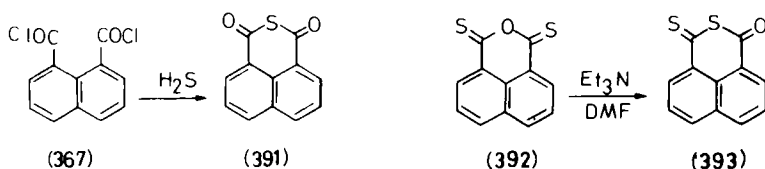
The stable tetra-phenyl-substituted  $\alpha, \alpha'$ -dehydroacenaphthylene [4,5-*cd*]thiapyran **390** is formed in high yield on heating 1,4,5,8-tetrabenzoylnaphthalene **387** or 1,2-diphenyl-5,6-dibenzoyl-acenaph-



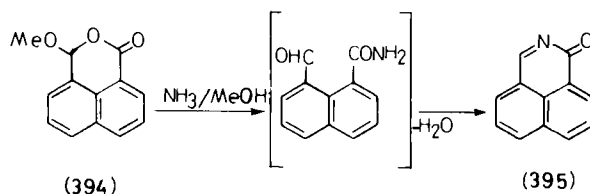


thylene **388** with phosphorus pentasulfide in pyridine (69JA3952; 69JA3953). It can also be formed by heating monothio ketone **389** over the melting point ( $240^\circ\text{C}$ ) or on treating it with hydrogen chloride, triphenyl phosphine, or tosyl chloride (69JA3953).

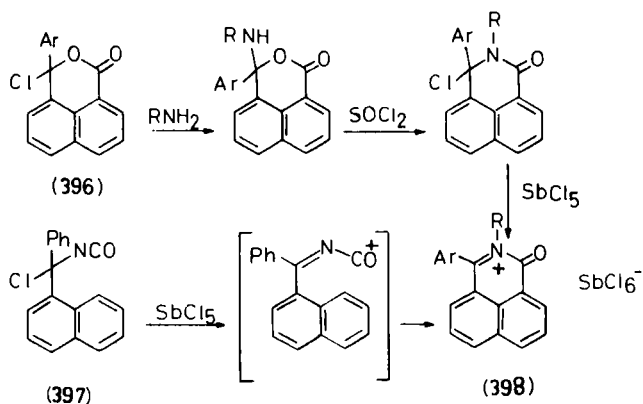
Diketone **388** and monoketone **389**, which are depicted in the scheme as intermediates, have been obtained independently and have also been converted into compounds **390** by all the previously listed methods. Two more examples of naphtho[cd]thiapyrans are thionaphthalic anhydride **391**, which is formed on interaction between naphthaloyl dichloride **367** and hydrogen sulfide (30RC657), and 2-oxo-9-thiononaphtho[cd]thiapyran **399**, obtained on base-catalyzed recyclization of dithione **392** (84JA6084).



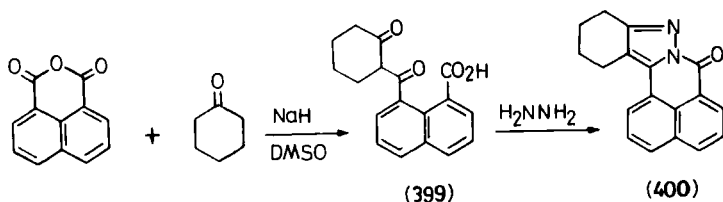
c. *Naphtho[cd]pyridines*. The general pathways in the synthesis of naphtho[cd]pyridines are recyclization of the corresponding naphtho[cd]pyran derivatives or cyclization of 1,8-dicarbonylnaphthalene derivatives. The interaction of 2-methoxynaphthalide **394** with ammonia gives rise to naphtho[cd]pyridine-2-one **395** (69JHC681).



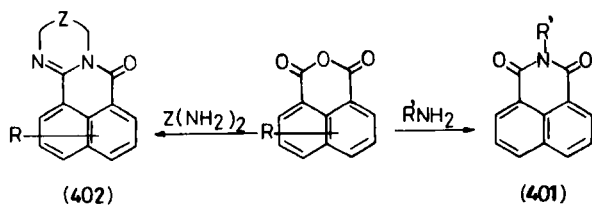
The reaction of 2-chloro-2-arylnaphthalides **396** with amines, followed by treatment with thionyl chloride and then antimony pentachloride (73KGS1127), or the intramolecular *C*-acylation of  $\alpha$ -chloro- $\alpha$ -(naphthyl-1)isocyanate **397** by the action of antimony pentachloride (84CB3211), leads to *N*-protonated or *N*-alkylated 9-aryl-2-oxonaphtho[*cd*]pyridinium salts **398**.



Peri-carboxy-substituted  $\beta$ -diketone **399**, obtained from naphthalic anhydride and cyclohexanone, is cyclized by hydrazine to the condensed heterocyclic system **400** (72TL4533). The most wide-spread representatives

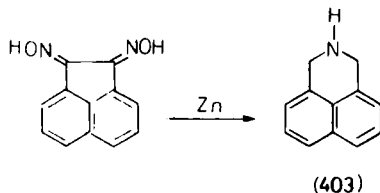


of naphtho[*cd*]azines are naphthaloimides **401** and their condensed nitrogen analogs **402**, which are formed on interaction of naphthalic anhydride or its derivatives with ammonia, amines, or diamines.

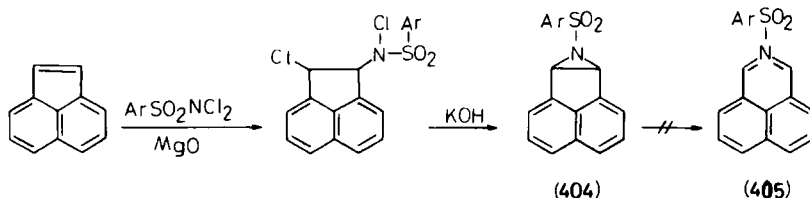


Information about syntheses of compounds **401** and **402** can be found in the Dashevskii monograph (66MI1) and in several other papers

(74KGS1049; 75ZOR1512, 75ZOR1517; 77ZOR1262, 77ZOR1958, 77ZOR2190; 82ZOR1997; 83KGS262). The reduction of naphthenequinone dioxime by zinc dust gives rise to 1*H*-2,9-dihydronaphtho[*cd*]pyridine **403** (66M11).



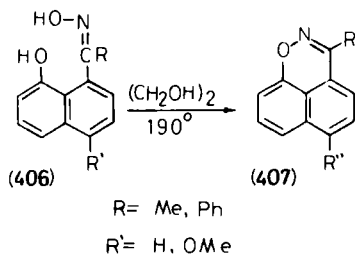
Compounds **405**, which are nitrogen analogs of  $\alpha,\alpha'$ -dehydronaphtho[*cd*]thiapyrans **383**, are unknown. However, their valence isomers **404**, obtained on interaction of acenaphthylene with *N,N*-dichlorosulfamides, have been described (80MI3).



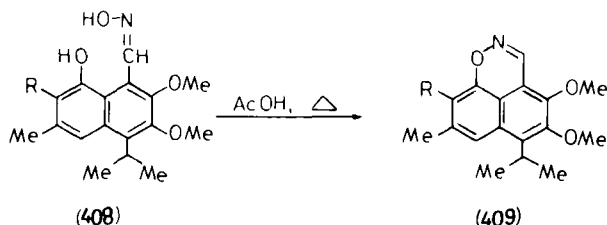
## E. PERI-HETEROCYCLES WITH SIX-MEMBERED HETERORING AND TWO HETEROATOMS

### 1. Heterocyclic Systems with 1,2-Heteroatoms

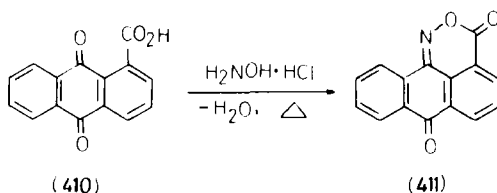
a. *Naphtho[de]-1,2-oxazines and Naphtho[cd]-1,2-oxazines*. Naphtho[*de*]-1,2-oxazines **407** are obtained by cyclization of peri-hydroxy ketone oximes **406**, which occurs on heating in ethylene glycol [71JCS(C)747; 83TH1]. Under these conditions, peri-hydroxynaphthaldehyde oxime **406**



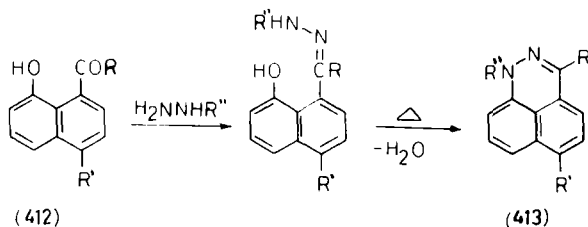
( $R = R' = H$ ) does not form a heterocyclic product, but is converted into 1,8-cyanohydroxynaphthalene [75JSC(P1)419], whereas gossypol and its derivative oximes **408** are easily cyclized into the corresponding naphtho[*de*]-1,2-oxazines **409** (38JA2166; 75JJC865).



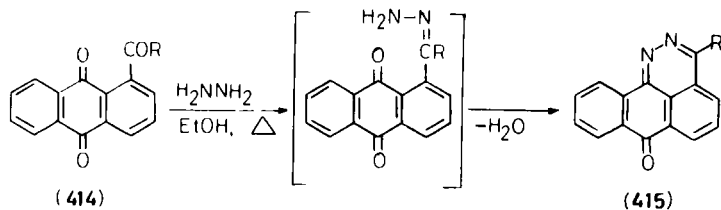
Peri-annulated heterocyclic systems **411** with the inverse heteroatom orientation are formed on heating anthraquinone-1-carboxylic acid **410** in aqueous solution of hydroxylamine hydrochloride (64MII).



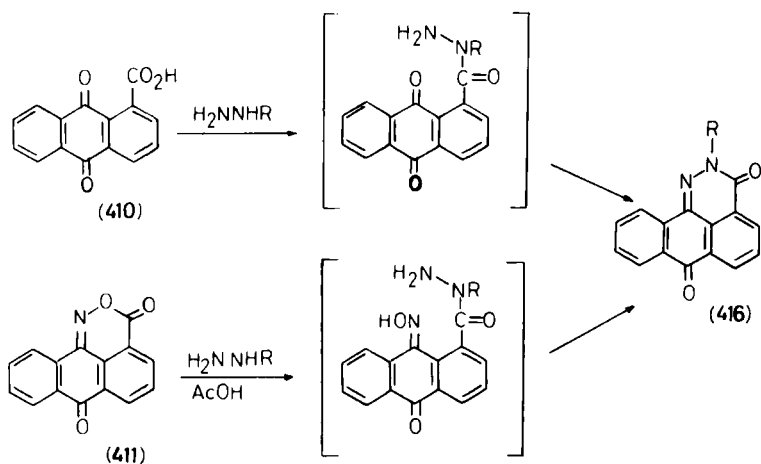
b. *Naphtho[de]pyridazines*. Precursors of naphtho[*de*]pyridazines are naphthaldehyde and naphthyl ketone hydrazones or naphthoic acid hydrazides having a substituent in the peri-position that is able to react intramolecularly with a nitrogen amine atom. Thus 1*H*-naphtho[*de*]pyridazine derivatives **413** are formed on heating peri-hydroxy-substituted naphthaldehydes and naphthyl ketones **412** with hydrazine or methylhydrazine in ethanol or ethylene glycol [71JCS(C)747; 75JCS(P1)419; 81ZOR627; 83MII].



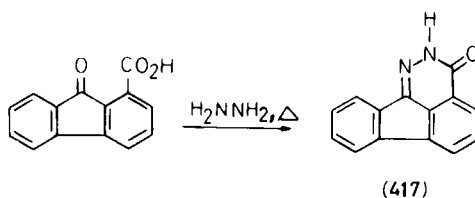
By analogy with peri-hydroxynaphthoyl compounds, 1-acylanthraquinones **414** are converted into pyridazinoanthrones **415** on heating with



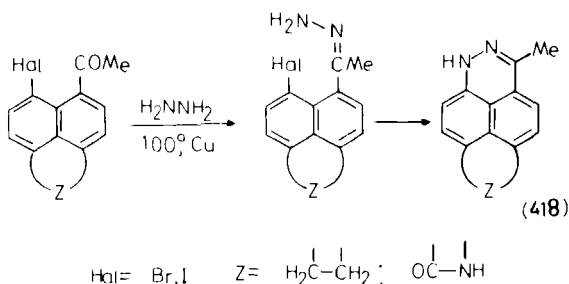
hydrazine hydrate (75JOC366). Heating anthraquinone-1-carboxylic acid **410** or oxazoneanthrone **411** with hydrazines gives rise to pyridazoneanthrones **416** (64MI1, 64ZOB2372; 75MI1).



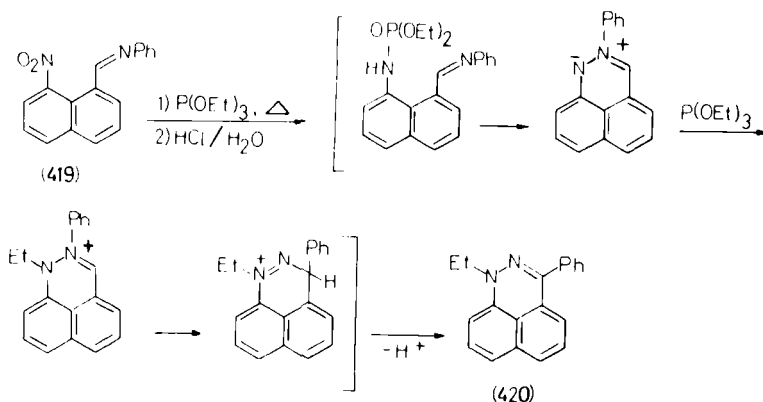
The same principle was applied to the synthesis of the pyridazinone derivatives **417** with a fluorine nucleus (63ZOB1974). One can use peri-



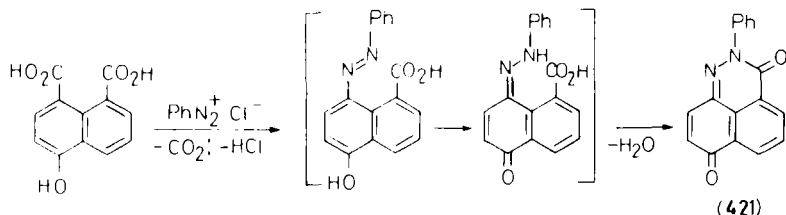
halogeno-substituted naphthyl ketones as the initial compounds for construction of naphtho[de]pyridazine nucleus. This approach is applied to synthesis of bis-peri-annelated heterocyclic systems **418** (73ZOR1067).



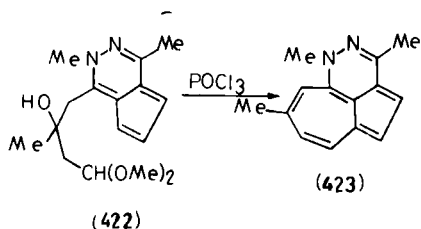
On lengthy heating of peri-nitronaphthaldehyde azomethine **419** with triethylphosphite, 1*H*-1-ethyl-3-phenylnaphtho[*de*]pyridazine **420** is



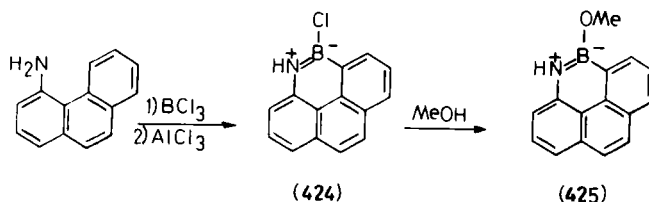
formed as a result of complex processes in reduction, heterocyclization, and rearrangement (86G405). Azocombination of 5-hydroxynaphthalic acid with phenyldiazonium chloride is accompanied by closure of the pyridazine ring, resulting in 2-phenylnaphtho[*de*]pyridazine-3,7-dione **421** (24CB1540).



The azulene-pyridazine derivative **423** has been obtained by attachment of a seven-membered carbocycle to cyclopentadieno[*d*]pyridazine **422** (78H387). Other azuleno[*de*]pyridazine derivatives have been similarly obtained (78H387). As for other peri-annulated heterocycles with

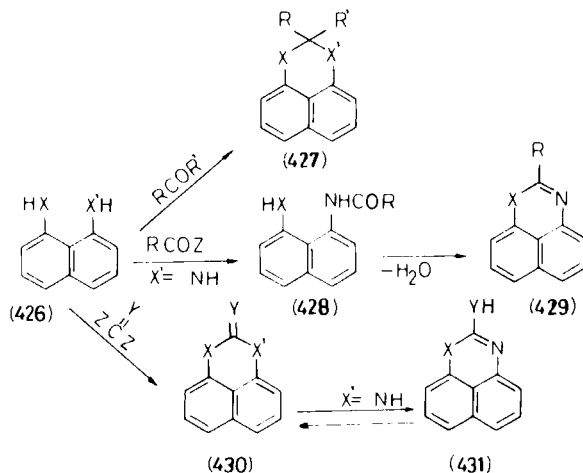


six-membered heteroring and 1,2-heteroatoms, 2-chloro- and 2-methoxytribenzo[*cde*]-2,1-borazines **424** and **425** have been described. These compounds are obtained from 1-aminophenanthrene (64JOC1757).



## 2. Heterocyclic Systems with 1,3-Heteroatoms

Known compounds in this class include mainly 1,3-oxazine, 1,3-thiazine, 1,3-diazine (perimidine)<sup>4</sup>, and to a lesser extent 1,3-dithiine and 1,3-dioxine peri-annulated derivatives. The general strategy for constructing such systems is based on heterocyclization of 8-hydroxy-, 8-mercapto-, or 8-amino-substituted 1-naphthylamines **426** ( $X' = \text{NR}$ )



<sup>4</sup> Syntheses of perimidines are exhaustively reported in a review by Pozharskii and Dalnikovskaya (81VK1559), which includes about 140 references. In this review, we formulate only the general principles of perimidine construction on the basis of data cited by Pozharskii and Dalnikovskaya (81VK1559).



and 1,8-dihydroxy or 1,8-dimercaptonaphthalenes **426** ( $X = X' = O$  or  $X = X' = S$ ).

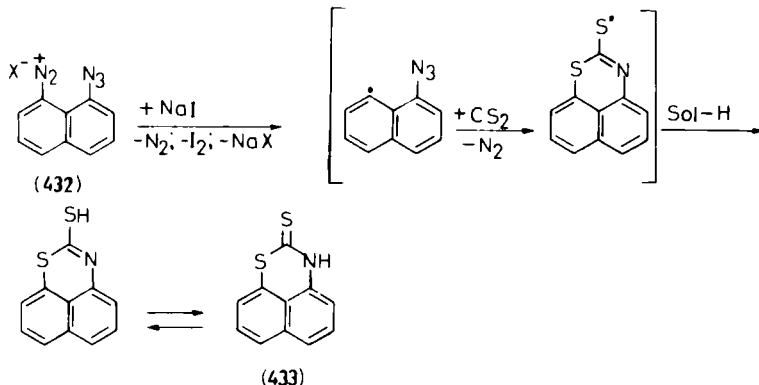
The character of a carbon atom in a meso-position of a newly formed heteroring is determined by the oxidation state of this atom in the cyclizing agent. Three types of cyclizing agents give, correspondingly, three types of peri-annelated azines [**427**, **429**, **430** (**431**)] and two types of dioxines and dithiines (**427**, **430**) ( $X = X' = O$  or  $X = X' = S$ ).

The treatment of 1,8-dihydroxynaphthalene **426** ( $X = X' = O$ ) with bromochloromethane and  $K_2CO_3$  in DMF gives rise to naphtho[*de*]-1,3-dioxine **427** ( $X = X' = O$ ,  $R = R' = H$ ) in good yield [83ZN(B)1000]. Acylation of 1,8-naphthalene dithiol **426** ( $X = X' = S$ ) with carboxylic acid chlorides in pyridine leads to mono-*S*-acyl-derivatives **427** ( $X = X' = S$ ,  $R = OH$ ) existing in a cyclic form. In sulfuric acid, the latter compounds are converted into naphtho[*de*]-1,3-dithiinium cations (77BCJ2193).

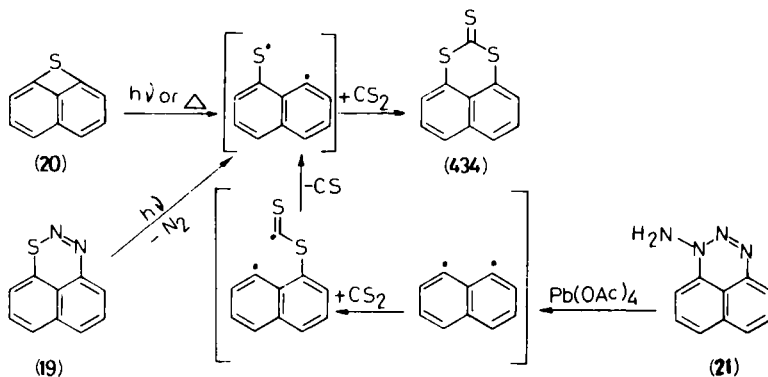
Interaction of *N*-substituted naphthylenediamines **426** ( $X = X' = NR$ ) with aldehydes and ketones gives 2,3-dihydroperimidines **427** ( $X = X' = NR$ ). The general method of synthesizing naphtho[*de*]-1,3-oxazines **429** ( $X = O$ ) [06CB(39)3331; 09CB4748; 39RTC125; 60CCC2831], naphtho[*de*]-1,3-thiazines **429** ( $X = S$ ) (22CB858; 31JA4046; 36JOC236; 43JCS487), and perimidines **429** ( $X = NR$ ) is based on cyclodehydration of the corresponding 8-substituted 1-(*N*-acyl)aminonaphthalenes **428**. Perimidines **429** ( $X = NR$ ) are often obtained immediately from 1,8-naphthylenediamines and carboxylic acids or their derivatives (anhydrides, acid chlorides, esters, amides, amidines, nitriles, etc.) without isolation of the intermediate compounds **428**. The reaction of 1,8-aminothionaphthol **426** ( $X = S$ ,  $X' = NR$ ), 1,8-naphthylenediamines **426** ( $X = X' = NR$ ), or 1,8-dimercaptonaphthalene **426** ( $X = X' = S$ ) with carbon sulfide gives rise to 2-thiono derivatives of naphtho[*de*]-1,3-thiazine **430** ( $X = Y = S$ ,  $X' = NR$ ) (38BRP496560), perimidine **430** ( $X = X' = NR$ ,  $Y = S$ ), and naphtho[*de*]-1,3-dithiine **430** ( $X = X' = Y = S$ ) (86CL551).

Potassium cyanate, carbonic and chlorocarbonic esters, phosgene, or urea are used as cyclizing agents in the synthesis of perimidine-2-one **430** ( $X = X' = NR$ ,  $Y = O$ ) and its derivatives from 1,8-naphthylenediamines. Naphtho[*de*]-1,3-dithiine-2-one **430** ( $X = X' = S$ ,  $Y = O$ ) is formed on interaction of 1,8-dimercaptonaphthalene with *N,N*-carbonyldiimidazole (86CL551). Perimidines **431** with an unsubstituted or substituted amino group in position 2 ( $X = Y = NH$  or  $Y = NR$ ) are obtained on interaction of 1,8-naphthylenediamines with bromocyanogen, cyanoamide, *S*-methylisothiurea, arylisothiocyanates, or dimethyltrichloromethylamine.

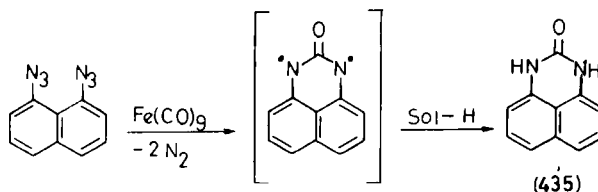
Syntheses based not only on compounds **426** but also on other 1,8-disubstituted naphthalenes have been described. Thus, decomposition of peri-diazonium-substituted azides **432** in carbon disulfide, proceeding by the free radical mechanism, yields naphtho[de]-1,3-thiazine-2-thiones **433**



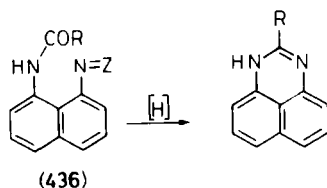
(81JOC4570). Photolysis or thermolysis of naphtho[bc]thiete **20** and naphtho[de]thiadiazine **19**, as well as oxidation of 1*H*-1-aminonaphtho[de]triazine **21** in carbon disulphide, also occurs by a free-radical mechanism which leads to naphtho[de]-1,3-dithiine-2-thione **434** in a mixture with other products of these conversions [79JA7684; 81JCS(P1)413].



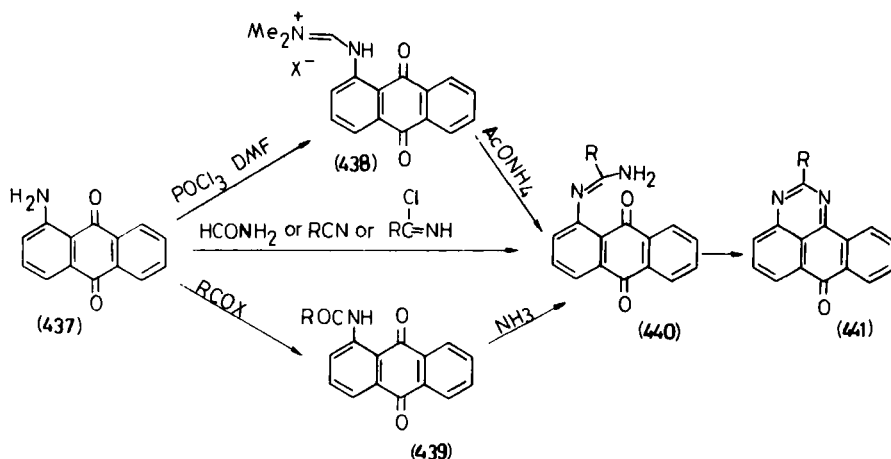
The reduction of 1,8-diazidonaphthalene by ferrous nonacarbonyl gives rise to perimidone **435** in low yield. Perimidines are also obtained on



reduction of 1-acylamino-substituted 8-nitroso-, 8-phenylazo-, or 8-azidonaphthalenes **436**.



Aromatization of dihydropyrimidines **427** to pyrimidine derivatives **429–431** ( $X = NR$ ) have been carried out (81UK1559). Benzologs of pyrimidine-6-ones, or so-called pyrimidinoanthrones (anthrapyrimidines) **441**, are well-known dyes. The precursors of these compounds are usually *N*-(anthraquinonyl-1)-amidines **440**, which are obtained from 1-aminoanthraquinone **437**, as described in the following paragraphs (83MI1).

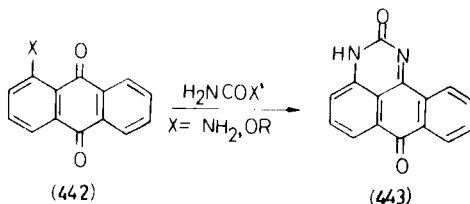


Pyrimidinoanthrones **441** ( $R = H$ ) unsubstituted in the heteroring may be obtained on interaction of 1-aminoanthraquinone **437** with formamide (79HOV414), with the Vilsmeier reagent followed by treatment of immonium salt **438** with ammonium acetate (63GEP1159456; 72GEP2124589; 73ZOR1494), or with formaldehyde and ammonia in the presence of an oxidizing agent (79HOV414).

Syntheses of 2-substituted pyrimidinoanthrones **441** ( $R = Alk, Ar$ ) are carried out by interaction of 1-aminoanthraquinone **437** with acylating agents ( $RCOX$ ), followed by treatment of the *N*-acylaminoanthraquinones **439** thus formed with ammonia or by reaction of **437** with nitriles or imi-

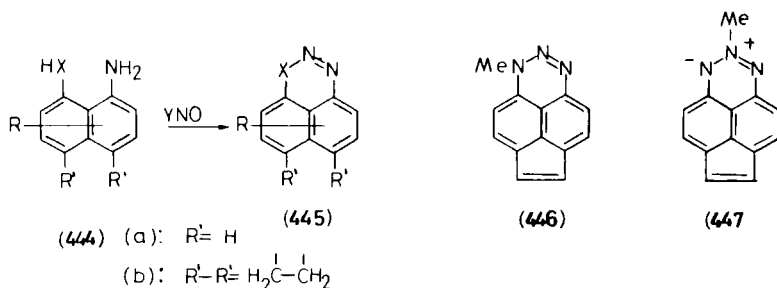
doylchloride (67BRP1061117; 79HOV414; 81GEP3001188). Heating 1-aminoanthraquinone with cyanoamide leads to 2-aminopyrimidinoanthrone **441** ( $R = NH_2$ ) (68ZVK462).

The interaction of 1-amino- or 1-chloroanthraquinones **442** ( $X = NH_2, Cl$ ) with urea or a urethan results in 2-oxypyrimidinoanthrone **443** (68MI1).



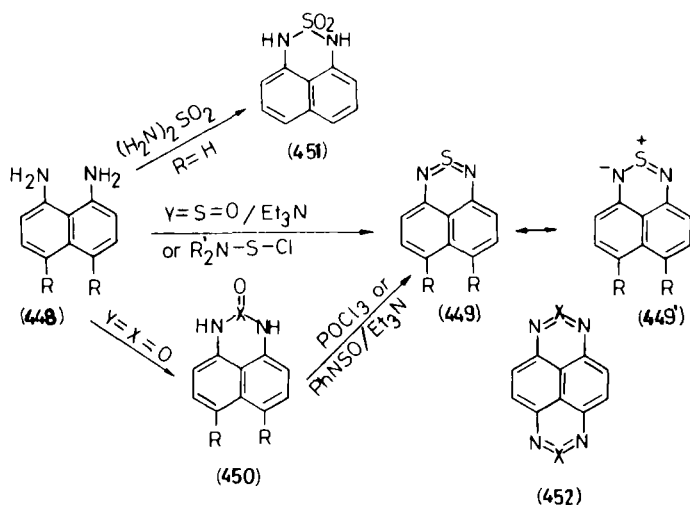
## F. PERI-HETEROCYCLES WITH SIX-MEMBERED HETERORING AND THREE HETEROATOMS

The interaction of 1,8-aminothionaphthol **444** ( $X = S$ ), *S,S*-dioxide **444** ( $X = SO_2$ ) or naphthylenediamine **444** ( $X = NR$ ) with diazotizing agents (nitrous acid, alkyl nitrites, nitrosoamines) gives rise to the corresponding naphtho[*de*]-1,2,3-thiadiazine **445** ( $X = S$ ) (79JA7684), *S,S*-dioxide **445** ( $X = SO_2$ ) [65AG(E)786; 67LA96], or 1*H*-naphtho[*de*]triazine **445a** ( $X = NR$ ) [1874CB306; 06JCS4; 09LA83; 40LA52; 49JA3002; 64JCS3005; 67CB1646; 69JCS(C)756]. This method was also used in the synthesis of acenaphthene derivatives of 1*H*-naphtho[*de*]triazine **445b** ( $X = NH$ ), which are *N*-alkylated followed by dehydrogenation to give 1-methyl and 2-methylacenaphthylene[4,5-*de*]-triazines **446** and **447** [67CC410; 70JCS(C)290].



As shown in Section II,C,1,b, photolysis or thermolysis of 1-azido-8-arylaazonaphthalenes gives rise to heterocyclization of these compounds, resulting in a mixture of mesoionic derivatives of naphtho[*de*]triazine **233**

and benzo[*cd*]indazoles **232**, the latter predominating. The construction of the naphtho[*de*]-2,1,3-thiadiazine nucleus is carried out by heterocyclization of 1,8-naphthylenediamines with sulfenating agents. Thus, the interaction of 1,8-naphthylenediamines **448** with sulfur dioxide or thionyl aniline (PhN = S = O) in the presence of triethylamine gives rise to naphtho[*de*]-2,1,3-thiadiazine derivatives **449** with a tetravalent sulfur atom. These derivatives may be considered also as mesoionic compounds **449'**. In the absence of triethylamine, the reaction is stopped at the stage of 1,3-dihydronaphtho[*de*]-2,1,3-thiadiazine *S*-oxides **450** (X = S), which then can be transformed into thiadiazines **449** by dehydrating agents (65CC57; 67CB2164; 78JA1235).

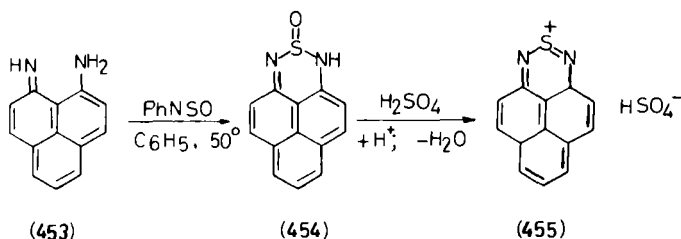


Following interaction of naphthylenediamine **448a** with thionyl chloride along with heterocyclization and dehydration, chlorination of the naphthalene nucleus occurs with formation of 4,6,7,9-tetrachloro derivative **449a** (65CB3196). However, reaction of **448a** with selenoyl chloride ( $\text{SeOCl}_2$ ) gives rise to a 1,3-dihydronaphtho[*de*]-2,1,3-selenodiazine-2-oxide **450a** (X = Se), which was not dehydrated into the corresponding selenodiazine, as for thiadiazine **449a** (79JA3306). Dehydrothiadiazines **449** may be obtained from 1,8-naphthylenediamine and piperidinosulfonyl chloride ( $\text{C}_5\text{H}_{10}\text{NSCl}$ ) [84JCS(P1)2591]. Unlike methods of heterocyclization just described, the oxidation state of the sulfur atom is changed from 2 to 4. Probably, the *N*-sulfonyl chloride plays the role of oxidant.

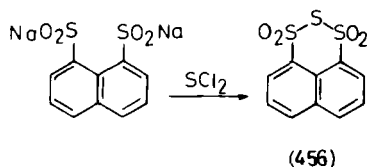
The reaction of 1,4,5,8-naphthylenetetramine with sulfenating or selenating agents ( $\text{SO}_2$ ,  $\text{C}_5\text{H}_5\text{NSCl}$ ,  $\text{SeOCl}_2$ ) leads to bis-peri-annulated heterocyclic systems **452** [78JA1235; 79JA3306; 84JCS(P1)2591]. Un-

der severe conditions (heating in diglyme), the interaction between 1,8-naphthylenediamine **448a** and sulfodiamide leads to 1*H*,3*H*-naphtho[*de*]-2,1,3-thiadiazine *S,S*-dioxide **451** [71JCS(C)993].

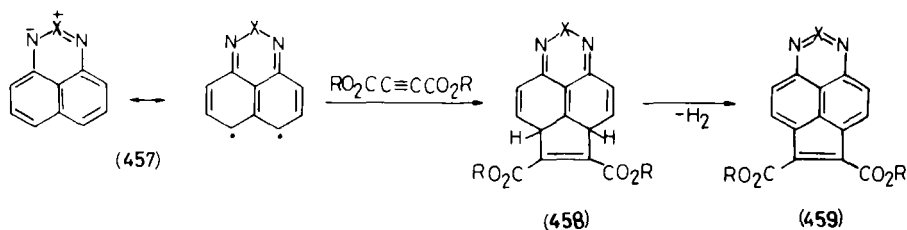
The reaction of 9-amino-1-phenaleneimine **453** with thionylaniline results in the corresponding thiadiazine *S*-oxide **454**, which is protonated in sulfuric acid and then dehydrated to give phenaleno[*cd*]-2,1,3-thiadiazinium salt **455** (81JOC675). Salt **455** was not isolated in a crystalline state,



but in solution, its spectral characteristics ( $^1\text{H}$  and  $^{13}\text{C}$ -NMR, UV-visible) have been registered. A synthesis of naphtho[*de*]trithiine 1,1,3,3-tetraoxide **456** from sodium 1,8-naphthalenedisulfinate and sulfur dichloride has been reported (81JOC4894).



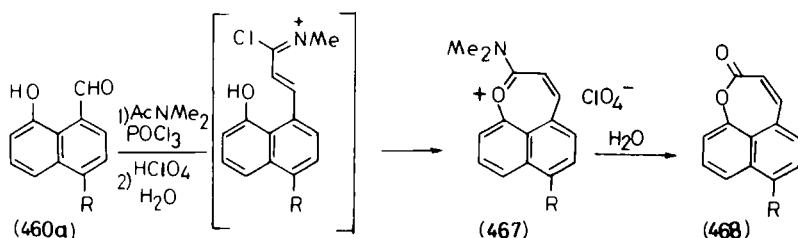
The most interesting compounds described in this paragraph are meso-ionic naphtho[*de*]triazines **457** ( $\text{X} = \text{NR}$ ) and naphtho[*de*]-2,1,3-thiadiazines **457** ( $\text{X} = \text{S}$ ), since these derivatives are disposed to undergo [12 + 2], cycloaddition in reactions with olefinic compounds. For instance, the reaction with acetylenedicarboxylates gives rise to adducts **458**, which are dehydrogenated spontaneously to the new heteroaromatic systems **459** with the aromatic  $14\pi$ -electron contour [75JCS(P1)556].



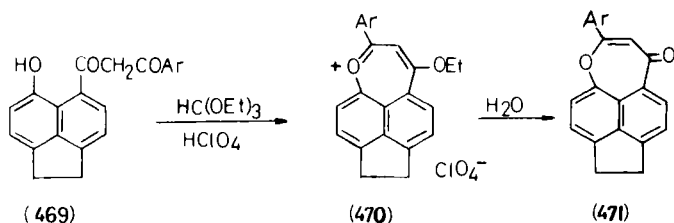
The result of a reaction between peri-hydroxynaphthaldehydes (**460**, R' = H) and malononitrile in the presence of bases depends on the nature of substituent R in position 4 and the ratio of components. With an equimolar ratio (for the cases with R = OH, OMe) the ring-opened product **461** is obtained, whereas with a twofold excess of malononitrile, 4H-

naphtho[*bc*]oxepine derivatives **465** are formed. 4-Unsubstituted peri-hydroxynaphthaldehyde **460** ( $R = R' = H$ ) always gives naphthooxepine **465** ( $R = H$ ) independent of the amounts of malononitrile. On heating in acetic acid, 4*H*-naphtho[*bc*]oxepines **465** are converted into 3-cyanonaphtho[*bc*]oxepines-2-ones **462**, whereas the interaction of **465** with acetyl chloride in pyridine leads to *N*-acetylminonaphtho[*bc*]oxepine **466** (88UP1).

2-Dimethylaminonaphtho[*bc*]oxepinium salts **467** have been obtained from peri-hydroxynaphthaldehydes **460a** and dimethylacetamide in the presence of phosphorus oxychloride. On hydrolysis, these salts are transformed to naphtho[*bc*]oxepine-2-ones **468** (URP114678; 86ZOR1487).

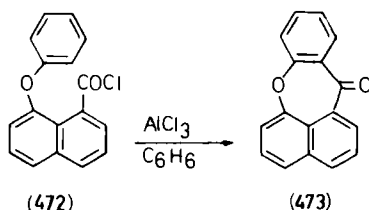


As shown in Section II,B,1,a, peri-hydroxy-substituted  $\beta$ -diketones of naphthalenes (**41**,  $R = CH_2COAr$ ), which may cyclize to either five- or seven-membered heterorings in acidic medium, form only a five-membered heterocycle, which results in naphtho[*bc*]furylium salts **42** [ $R = CH=COHAr$ ]. If five-membered ring-closure is hindered, then seven-membered ring-closure becomes possible. Such conditions are a reality for acenaphthene peri-hydroxy- $\beta$ -diketones **469**, since there are distortions of the valence angles because of the bridge in the peri-positions of the naphthalene nucleus. Closure of the second five-membered ring is hindered. So, interaction of acenaphthene peri-hydroxy- $\beta$ -diketones **469** with ethylorthoformate and perchloric acid leads to 2-aryl-4-ethoxyacenaphtho[4,5-*bc*]oxepinium salts **470** in high yields. These are hydrolyzed easily to 2-arylacenaphtho[4,5-*bc*]oxepine-4-ones **471** (89MI2).

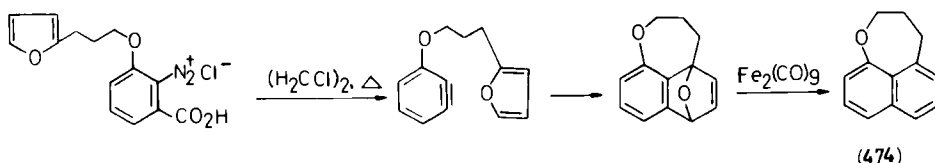




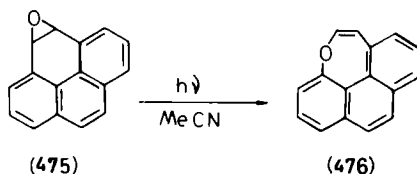
Naphtho[*bc*]oxepine-4-one benzolog **473** was obtained in a yield of 10% from 8-phenoxy-1-naphthoic acid chloride as a result of intramolecular



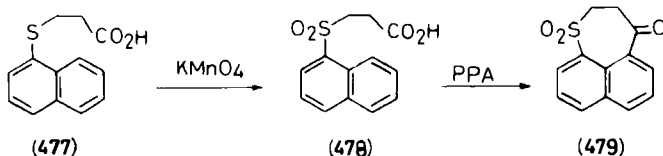
C-acylation by the action of aluminum chloride (79BCJ3314). The unusual pathway to construction of 2,3,4-trihydronaphtho[*bc*]oxepine **474** is based on the intramolecular cycloaddition of a furan fragment to a benzyne (86AJC635).



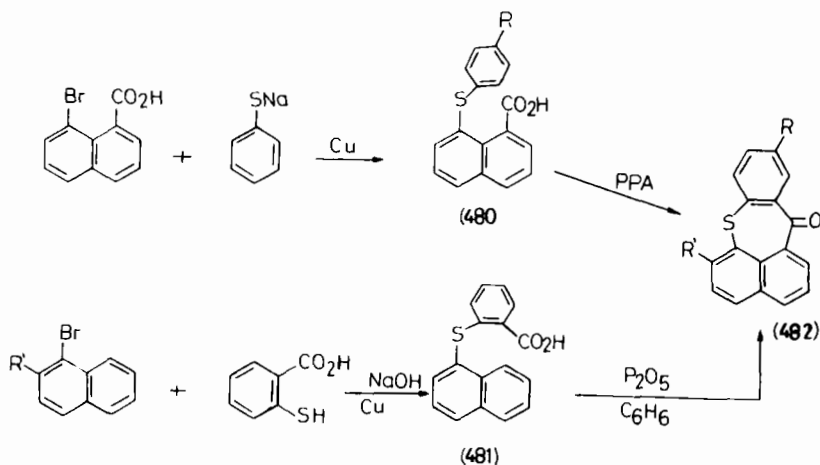
On irradiation, 3,4-dihydropyrene epoxide **475** undergoes a ring expansion, resulting in tribenzo[*bcd*]oxepine **476** (79T1059).



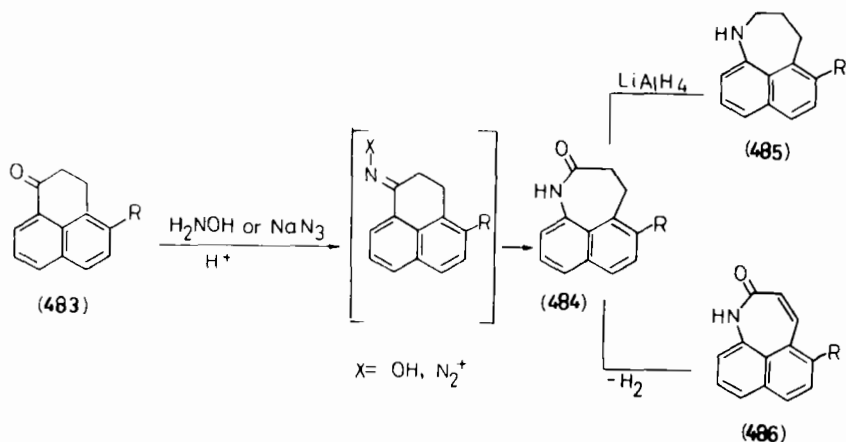
b. *Naphtho[bc]thiepines*. The simplest approach to construction of naphtho[*bc*]thiepines is the seven-membered ring-closure in 3-(1'-naphthyl)-mercaptopropionic acid **477**. This method was applied to the synthesis of 2,3-dihydronaphtho[*bc*]thiepine-4-one *S,S*-dioxide **479**. Oxidation to *S,S*-dioxide **478** precedes heterocyclization; this step is necessary to suppress the electron-donor effect of the sulfur atom, which could take part in ortho-acylation to give a six-membered ortho-annulated heteroring [71CI(M)357].



Benzo[*f*]annelated naphtho[*bc*]thiepine-4-one derivatives **482** are obtained by cyclization of 8-arylmercapto-1-naphthoic or 1-naphthylmercaptosalicylic acids **480** and **481** (38M440; 75CCCC1604; 84JHC1737). In the latter case, in order to avoid ortho-acylation, the ortho-position (towards the sulfur atom) of the naphthalene nucleus is blocked by a substituent.



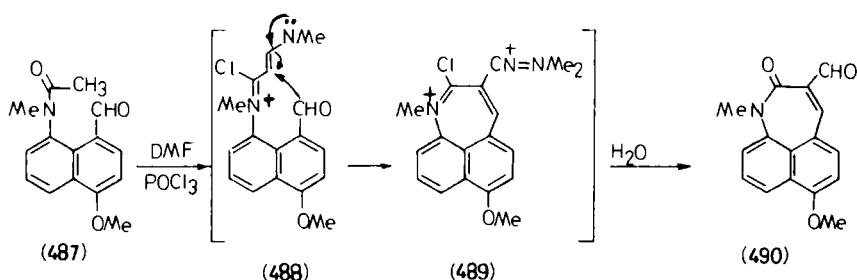
c. *Naphtho[bc]azepines*. The construction of a seven-membered nitrogen heterocycle is based on transformations of 2,3-dihydrophenalene-1-one **483** by the Beckmann or Schmidt reactions, leading to 3,4-dihydronaphtho[*bc*]azepine-2-ones **484** [52JCS843; 69JCS(C)1642; 71



JCS(C)1607; 76JHC371]. In the Schmidt reaction, the second isomer, 9,10-dihydronaphtho[*cd*]azepine-2-one, is formed in small amounts. This

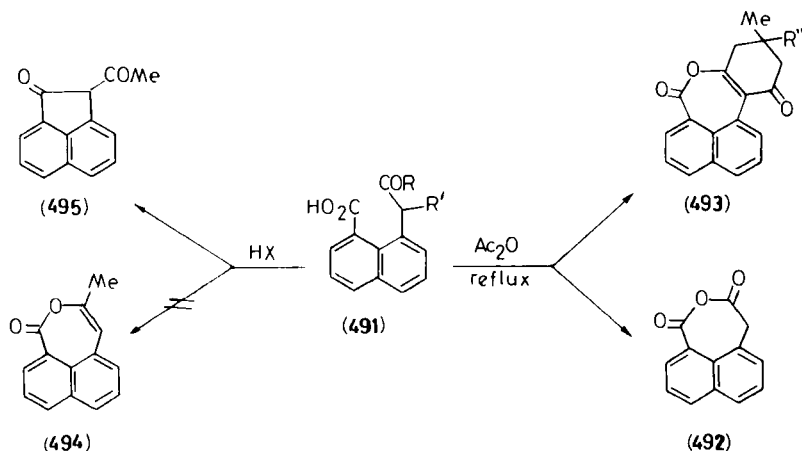
compound is the result of the alternative cleavage of a C—C bond in the transformation of the six-membered carbocycle into the seven-membered heterocycle (76JHC371).

The reduction of azepinone **484** leads to 1,2,3,4-tetrahydroderivative **485**, whereas dehydrogenation of **484** by chloroanil results in 1*H*-naphtho[*bc*]azepine-2-one **486** (76JHC371). The interesting conversion resulting in 1*H*-1-methyl-3-formyl-7-methoxynaphtho[*bc*]azepine-2-one **490** occurs on interaction of 4-methoxy-8-(*N*-methyl-*N*-acetyl)aminonaphthaldehyde **487** with the Vilsmeier reagent (86ZOR2394). It was assumed that compounds **488** and **489** are intermediates in this reaction.

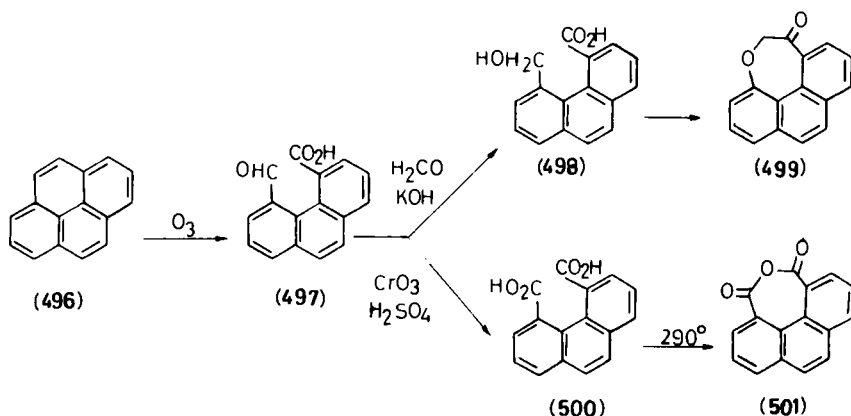


## 2. Naphtho[*cd*]annelated Heterocycles

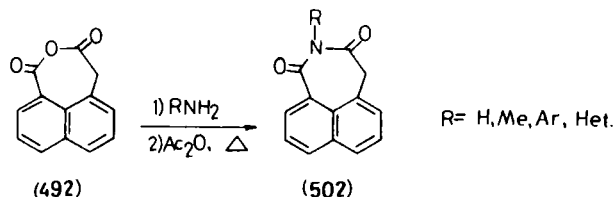
a. *Naphtho[*cd*]oxepines*. A few known representatives of the naphtho[*cd*]oxepine series **492** and **493** are obtained by heterocyclization of peri-carboxy-substituted homoacids **491** ( $R = OH$ ,  $R' = H$ ) or cyclic  $\beta$ -diketones **491** (74AJC2209).



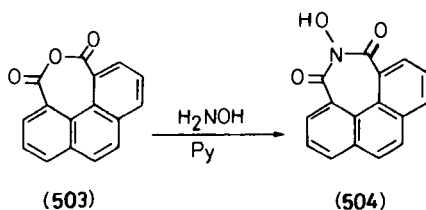
An attempted synthesis of 9-methylnaphtho[*cd*]oxepine-2-one **494** by heterocyclization of 8-acetyl-1-naphthoic acid **491** ( $R = \text{Me}$ ,  $R' = \text{H}$ ) has failed. In acidic medium or on heating acid **491** to  $150^\circ\text{C}$ , as well as under formation conditions for the acid chloride or ester from acid **491**, 2-acetylnaphthene-1-one **495** is obtained (79ZOR1562). A synthesis of tribenzo[*cde*]oxepine derivatives **499** and **501** has been described as resulting from heterocyclization of the products of reduction (**498**) or oxidation (**500**) of 4-formyl-5-carboxyphenanthrene **497**. The latter compound was obtained on ozonolysis of pyrene **496** [71JCS(C)729].



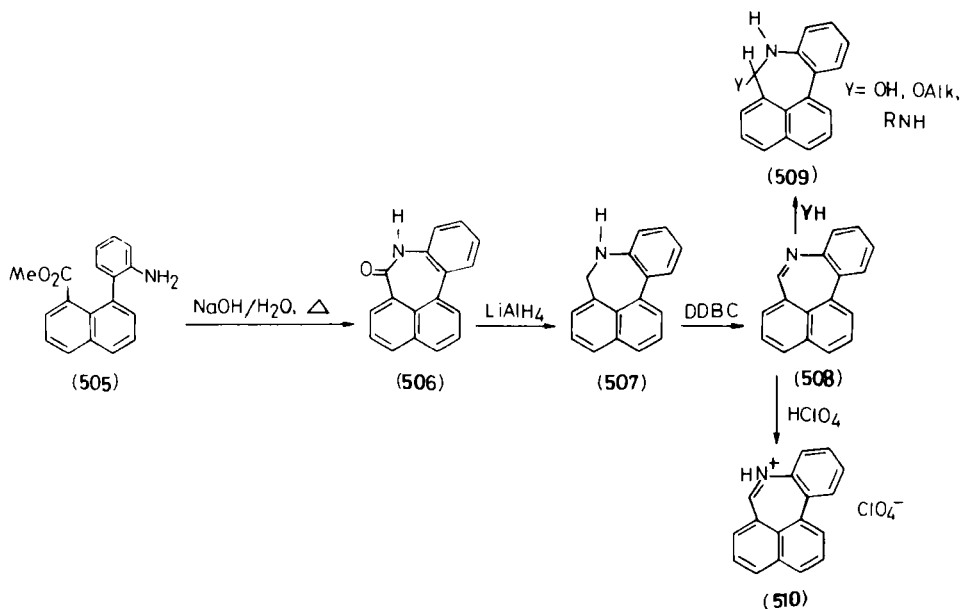
b. *Naphtho[cd]azepines*. The simplest known naphtho[*cd*]azepines are the so-called homonaphthaloylimides **502**, which are formed on interaction of homonaphthalic anhydride **492** with ammonia or primary



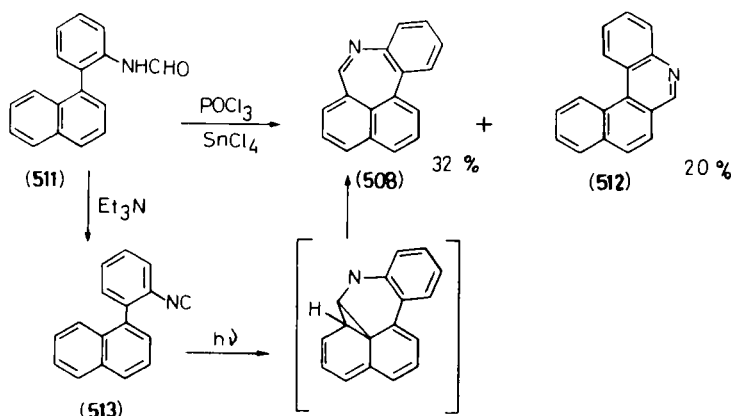
amines (74AJC2209; 86SC547). The reaction between phenanthrene-4,5-dicarboxylic acid anhydride **503** and hydroxylamine gives *N*-hydroxyimide **504** [71JCS(C)729].



A benzolog of 1*H*-naphtho[*cd*]azepine-2-one **506** is obtained by cyclization of 1-(2'-amino)phenyl-8-methoxycarbonylnaphthalene **505** (71AJC835). The reduction of azepinone **506** to azepine **507**, followed by dehydrogenation with dichlorodicyanobenzoquinone (DDBQ) leads to benzo[*f*]naphtho[*cd*]azepine **508**. The latter compound easily adds water, alcohol, or amines to a C=N bond, resulting in adducts **509**, whereas treatment with perchloric acid gives rise to perchlorate **510** (71AJC835).

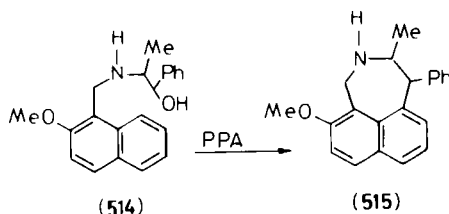


Benzo[*f*]naphtho[*cd*]azepine **508** can be obtained also on treatment of 1-(2'-formylamino)phenylnaphthalene **511** with phosphorus oxychloride



or stannic tetrachloride (78S205). It can also be obtained photochemically via isocyanide **513** [79JCS(P1)1070]. In the former case, along with pericyclization, ortho-cyclization takes place, resulting in benzo[*b*]phenanthridine **512**.

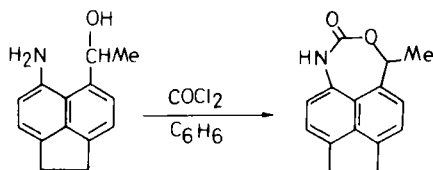
On chromatographic separation of isomers **508** and **512**, partial oxidation of azepine **508** leads to azepinone **506**. Aminocarinol **514**, having the blocked  $\beta$ -position, is cyclized into tetrahydronaphtho[*bc*]azepine **515** in polyphosphoric acid (81H469).



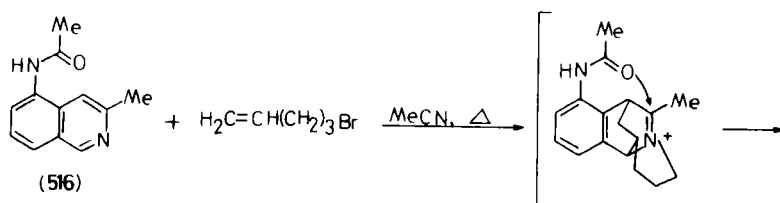
## H. PERI-HETEROCYCLES WITH SEVEN-MEMBERED HETERORING AND TWO HETEROATOMS

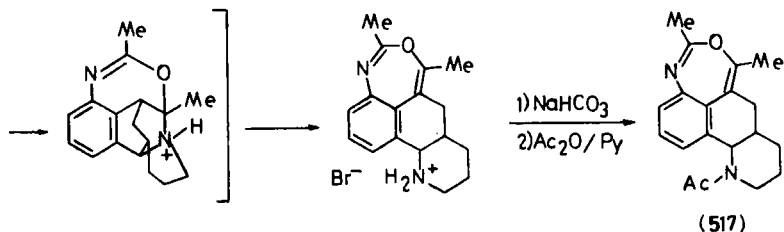
### 1. Naphtho[*ef*]-3,1-oxazepines

The treatment of 5-( $\alpha$ -hydroxy)ethyl-6-aminoacenaphthene with phosgene in boiling benzene leads to the ring closure of 3,1-oxazepine (66ZOR148). The partially hydrogenated derivative **517** is formed as the



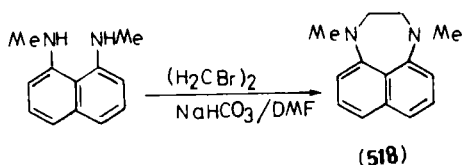
result of interaction between 3-methyl-5-acetamidoisoquinoline **516** and 5-bromopentene by several steps.



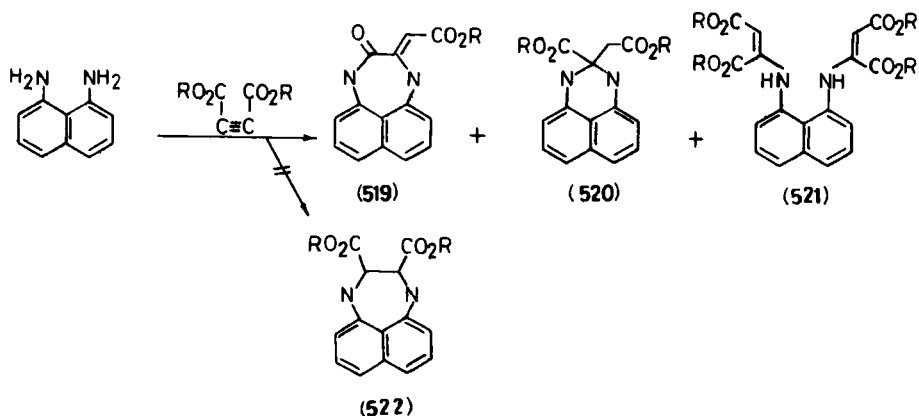


## 2. Naphtho[ef]-1,4-diazepines

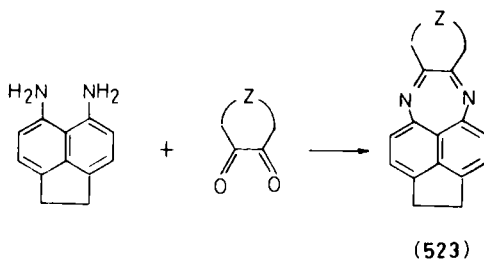
Linking nitrogen atoms of the amino groups in 1,8-naphthylenediamine and its derivatives by a chain of two carbon atoms is the simplest principle for constructing naphtho[ef]-1,4-diazepine nucleus. The interaction of 1,8-di(*N*-methyl)aminoaphthalene with 1,2-dibromoethane gives rise to 1,4-dimethyl-1,2,3,4-tetrahydronaphtho[ef]-1,4-diazepine **518** in a yield of 25% [81JCS(P1)2840].



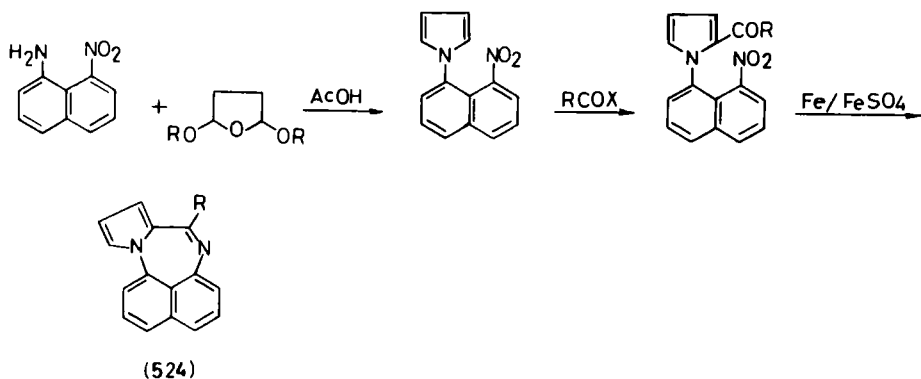
The reaction of 1,8-naphthylenediamine with acetylenedicarboxylic ester leads to the mixture of compounds **519–521**. The major products of this reaction are compounds **520** and **521**, whereas 1,4-diazepine derivatives **519** are formed in a yield of 1% only (86MI1). Structure **522** proposed for one of the products is incorrect (NK2161, 62NKZ597; 83BCJ2338; 86MI1).



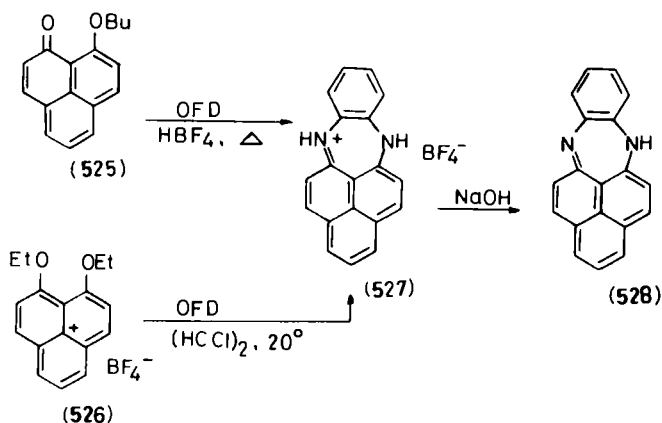
Condensation of 4,5-diaminoacenaphthene with cyclic  $\alpha$ -diketones (acenaphthenequinone, phenanthrenequinone) gives rise to b-side annelated acenaphtho [4,5-*ef*]-1,4-diazepine derivatives **523** (11CB2852;



33CB1230, 33JIC679; 54JCS4436). The original pathway to the new heterocyclic system **524** having a naphtho[*ef*]-1,4-diazepine nucleus has been described (86JHC65).

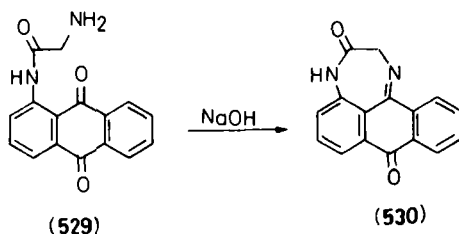


The reaction of peri-butoxyphenalenone **525** or peri-diethoxyphenalenium borofluoride **526** with ortho-phenylenediamine (OFD) under



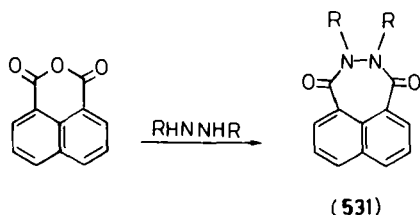


mild conditions results in peri-annelated diazepinium salt **527**, which is deprotonated easily to the corresponding base **528** (78CZ199; 79JOC1704). Benzolog naphtho[*ef*]-1,4-diazepine-2,7-dione **530** is the result of a transformation of 1-( $\alpha$ -aminoacetyl)aminoanthraquinone **529** by the action of alkaline hydroxide (67M1537).

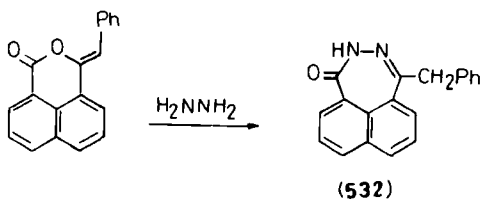


### 3. Naphtho[*de*]-1,2-diazepines

There are known methods for constructing a naphtho[*de*]-1,2-diazepine nucleus by ring expansion on interaction of naphtho[*cd*]pyran derivatives with hydrazines. Thus, the reaction of naphthalic anhydride with hydrazines leads to 3,10-dioxo derivatives of naphtho[*de*]-1,2-diazone **531** (12G757; 25HCA810; 75MI2; 76MI1).

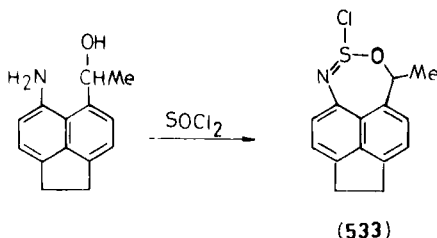


The interaction between 2-benzylidenenaphtho[*cd*]pyran-9-one and hydrazine gives rise to 3-benzyl-1*H*-naphtho[*de*]-1,2-diazepine-10-one **532** [81IJC(B)573, 81IJC(B)456].



# I. PERI-HETEROCYCLES WITH SEVEN-MEMBERED HETERORING AND THREE HETEROATOMS

3,2,1-Oxathiadiazepine derivative **533** has been obtained in good yield on interaction of 5-(hydroxy)ethyl-6-aminoacenaphthene with thionyl chloride (66ZOR148).



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# 1-Hydroxypyrroles, 1-Hydroxyindoles and 9-Hydroxycarbazoles

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## I. Introduction

Although 2,5-dimethyl-1-hydroxypyrrole was synthesized in 1886 by Knorr, the parent 1-hydroxypyrrole was obtained only 90 years later. These compounds have not been widely investigated. The corresponding radicals, the pyrrole 1-oxyls, their 2,5-dihydro derivatives, and particularly the pyrrolidine 1-oxyls, if the adjacent positions to the nitrogen atom are substituted, can be stable. Many of these pyrrolidines have been prepared and used as "spin labels." Only one 1-hydroxypyrrole, an antitumor antibiotic, has so far been isolated from living systems.

Many early claims of having prepared simple 1-hydroxyindoles have proved to be unfounded, although the unusually stable 1-hydroxy-2-phenylindole was obtained in 1895. 1-Hydroxyindole itself polymerizes on attempted isolation, while O-acylation, O-alkylation, or the presence of substituents greatly stabilizes the molecule. One 1-hydroxyindole antibiotic has been identified and is the only 1-hydroxyindole derivative isolated from natural sources so far. In contrast, a substantial number of 1-methoxyindoles occurs in various plants, and some of these may inhibit tumor formation in mammals. The biochemistry of these compounds, which include 1-methoxy-indoles, -indolines and -2-oxindoles, has not been widely investigated and could be a very fruitful area for new research which might well lead to novel medicinal agents and other useful compounds.

Carbazole can be oxidized to the 9-oxyl radical, which has been identified in fish liver; it may be related to tumor production. A small number of 9-hydroxycarbazoles has been made.

## II. 1-Hydroxypyrroles

### A. STRUCTURE AND SPECTRA

No molecular structure study has so far been published on any 1-hydroxypyrrole. The UV spectrum of 1-hydroxypyrrole **1** has not been



described, but the 2,5-di-*t*-butyl derivative shows  $\lambda_{\max} = 217 \text{ nm}$  ( $\epsilon$  8400) in methanol, unchanged by acid or alkali (70BSF4330). Its IR spectrum shows a series of OH bands between  $3520$  and  $3100 \text{ cm}^{-1}$  that are absent in 1-acetoxypyrrole [76ZN(B)599], and 2-cyano-1-hydroxypyrrole shows a broad band between  $3400$  and  $2800 \text{ cm}^{-1}$  [76JA1478].

The  $^1\text{H}$ -NMR spectra (Table I) show no evidence of tautomerism of 1-hydroxypyrroles to *2H*- or *3H*-pyrrole 1-oxides and are similar to those of corresponding pyrroles. The hydroxyl proton is not always seen, as in the case of 1-hydroxyindole, and is easily exchanged out by deuterium oxide. The  $^1\text{H}$ -NMR spectrum of 2-cyano-2-methyl-*2H*-pyrrole 1-oxide (**2**) in dimethyl sulfoxide (DMSO) was unambiguous (Table I), but in deuteriochloroform, the 3- and 4-protons appeared at the same position.

Very few  $^{13}\text{C}$ -NMR spectra have been reported. 1-O-Cyano-2,3,4,5-tetrakis(trifluoromethylthio)pyrrole shows the 2-, 3-, and OCN carbon atoms at 131.38, 124.27, and 125.18 ppm, respectively (85CB4588), and the 2-, 3-, 4-, and 5-C atoms of the 1-hydroxypyrrole ring in chromoxymycin (Section II,E) appear at 130.5, 96.9, 105.3, and 119.6 ppm, respectively (85TL3273). The structure of 2-cyano-2-methyl-*2H*-pyrrole 1-oxide (**2**) was established (76JA1478) from its  $^{13}\text{C}$  spectrum: 2-C, 66.8s; 2-CN, 117.8s; 2-Me, 24.7q; 3-C, 129.4d; 4-C, 116.8d; 5-C, 147.4d.

The mass spectrum fragmentation patterns of 1-hydroxypyrroles show the molecular ions followed by an abundant peak at  $(\text{M} - \text{OH})^+$  [72JOC1561; 76JCS(P1)2259], as in 1-hydroxyindoles [70JCS(C)1067]. The 1-O-cyanopyrrole mentioned previously shows a 2% molecular ion and a 95% peak corresponding to  $(\text{M} - \text{OCN})^+$  (85CB4588). The fragmentation of 2,4,5-triphenyl-*3H*-pyrrol-3-one 1-oxide (**9**) has been studied in detail [77JCS(P2)412], and one pathway shows the consecutive loss of 2 mol of carbon monoxide.

## B. GENERAL PROPERTIES AND CHEMICAL REACTIVITY

1-Hydroxypyrrole **1** is a colorless liquid, which has not been analyzed, and which decomposed on attempted distillation under high vacuum [76ZN(B)599]. Its  $^1\text{H}$ -NMR spectrum, and those of other 1-hydroxypyrroles (72JOC173, 72JOC1561), gave no indication of tautomer-

TABLE I  
THE <sup>1</sup>H-NMR SPECTRA OF SOME 1-HYDROXYPYRROLES IN δ (J IN HERTZ) FROM INTERNAL Me<sub>4</sub>Si

Substituents <sup>a</sup>	Solvent	Ring protons				HO	Me	Reference
		2	3	4	5			
—	CCl <sub>4</sub>	6.60t	5.86t	5.86t	6.60t	6.17	—	76ZN(B)599
O-Ac	CDCl <sub>3</sub>	6.66t	6.09t	6.09t	6.66t	—	—	76ZN(B)599
2-CN	CDCl <sub>3</sub>	—	6.55	5.96	6.90	7.56 <sup>b</sup>	—	
				J <sub>3,4</sub> 3.5, J <sub>4,5</sub> 2.5, J <sub>3,5</sub> 1.5				76JA1478
2,5- <i>t</i> -Bu	CCl <sub>4</sub>	1.33 <sup>c</sup>	5.42	5.42	1.33 <sup>c</sup>	5.55 <sup>d</sup>	—	70BSF4330
2-CN-3-Me	CDCl <sub>3</sub>	—	—	5.90	6.84	8.07	2.10	76JA1478
2-CN-4-Me	CDCl <sub>3</sub>	—	6.40	—	6.75	7.00	2.24	76JA1478
2-CN-5-Me	CDCl <sub>3</sub>	—	6.55	5.80	—	7.80	2.20	76JA1478
2,3-Ph <sub>2</sub>	CDCl <sub>3</sub>	—	—	6.23	6.86	not seen	—	72JOC1561
3-Ph-2-CO <sub>2</sub> Et	CDCl <sub>3</sub>	—	—	5.97	6.93	10.02 <sup>b</sup>	—	72JOC1561
				J <sub>4,5</sub> 2.8				
3-Ph	CDCl <sub>3</sub>	6.61m	—	6.19m	6.86m	10.01 <sup>b</sup>	—	72JOC1561
Me <sub>2</sub>	CCl <sub>4</sub>	—	—	5.51	6.3	7.9	1.9s, 2.0s	80TL2893
				J <sub>4,5</sub> = 3				
A	(CD <sub>3</sub> ) <sub>2</sub> SO	—	6.39	6.24	8.08	—	1.81s	76JA1478
				J <sub>3,4</sub> 10				
B	C <sub>5</sub> D <sub>5</sub> N	—	5.37	6.90	—	?	—	85TL3273
			J <sub>3,4</sub> 4					

<sup>a</sup> A, 2-Cyano-2-methyl-2*H*-pyrrole 1-oxide; B, Chromoxymycin; see Section II, E.

<sup>b</sup> Exchanges in D<sub>2</sub>O.

<sup>c</sup> *t*-Bu.

<sup>d</sup> Broad.

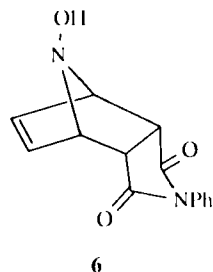
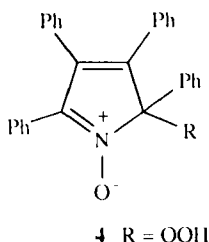
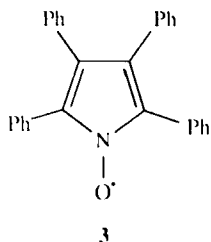
ism to the 2*H*- or 3*H*-pyrrole 1-oxides. However, 1-hydroxy-2,3-diphenylpyrrole in chloroform with deuterium oxide exchanged the 5-proton five times faster than the 4-proton, exchange being complete in 2 hr (72JOC1561). Protonation of the ring at these positions clearly occurs, possibly catalyzed by traces of hydrogen chloride in the chloroform, but the possible intermediacy of tautomeric forms is still an open question.

2,5-Dimethyl-1-hydroxypyrrole was first described as an oil (1886-LA290) and later (14CR1686) as an unstable solid which was poorly characterized. The zinc and hydrochloric acid reduction of this substance, and also of 2,5-dimethylpyrrole, gave the same (presumably) 2,5-dihydro-2,5-dimethylpyrrole (14CR1686). 1-Hydroxy-2,3,5-triphenyl- (34JA2774) and -2,3,4,5-tetraphenyl-pyrrole (68BSF4679) are stable compounds. Substituents clearly stabilize the 1-hydroxypyrrole ring.

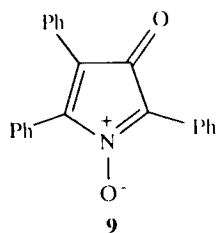
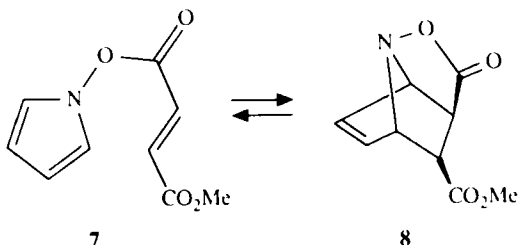
1-Hydroxypyrroles are readily acetylated and benzoylated [34JA2774, 72JOC1561; 76ZN(B)599; 84CC630] to the more stable O-acyl derivatives, and some 4-O-toluenesulfonates, O-methyl and O-benzyl (34JA2774, 76JHC465) and 4-O-nitrobenzyl ethers have been prepared (72JOC173). Acyl derivatives can be hydrolyzed back to the 1-hydroxypyrroles (34JA2774). 1-Hydroxypyrroles are readily deoxygenated to the corresponding pyrroles by zinc and acetic acid [60AC(R)1627; 68BSF4679; 70BSF4330], iron and acetic acid, or Raney nickel (78JHC537). Boiling methanol converts 2-cyano-1-hydroxypyrrole to 2-cyanopyrrole (72JOC173), and a complex 1-hydroxypyrrole gave the corresponding pyrrole on 12-hr refluxing with ethanolic hydrazine hydrate (79JHC203). The 1-hydroxy group is not affected by lithium aluminum hydride or sodium borohydride in the cases so far reported.

The nitrile function of 1-benzyloxy-2-cyanopyrrole was not reduced by stannous chloride-hydrochloric acid under Steven's conditions nor by lithium triethoxyaluminum hydride, but when diisobutylaluminum hydride was used, both it and the 1-methoxy analogue gave the corresponding 1-alkoxypyrrole-2-aldehydes (76JHC465). Attempted debenzoylation of the previously mentioned 1-benzyloxypyrroles to the 1-hydroxy compounds failed. 1-Methoxy- and 1-(4-methoxybenzyloxy)pyrrole-2-aldehydes gave the corresponding 1-alkoxydipyrromethenes when condensed with polyalkylpyrroles in the presence of hydrogen bromide, but some dealkylation took place, and the products were very hard to purify (76JHC465).

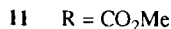
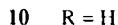
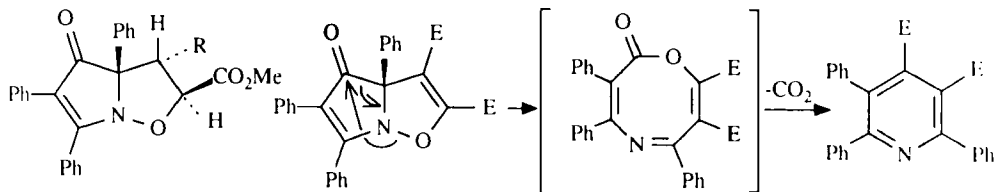
The oxidation of 1-hydroxy-2,3,4,5-tetraphenylpyrrole in benzene by lead(IV) dioxide (68BSF4679) gave the radical **3** which was reduced back to the hydroxypyrrole by lithium aluminum hydride. Photosensitized oxidation gave the peroxyxynitrone **4**, which was reduced by potassium iodide in acetic acid to **5** (68BSF4679). *N*-Phenylmaleimide reacts at room temperature with 1-hydroxypyrrole to give the Diels-Alder-type adduct **6**,



confirming the idea that the inductive effect of the oxygen atom would reduce the aromaticity and thereby increase the dienoid activity of the ring. The stereochemistry of the adduct was deduced [76ZN(B)599] from its  $^1\text{H-NMR}$  spectrum. Acetylation and benzylation gave the expected *O*-acyl derivatives, also obtained from *N*-phenylmaleimide and the corresponding 1-acyloxypyrroles. Methyl 1-pyrrolylfumarate **7** from 1-hydroxypyrrole and *E*-3-(methoxycarbonyl)acryloyl chloride, in refluxing toluene, gave in 20 min a 2.5 : 1 equilibrium mixture with the intramolecular adduct **8** (84CC630), while effecting the reaction in this solvent at  $38^\circ$  over three weeks gave the adduct in 68% yield; the use of high pressures would doubtless facilitate this addition. 3*H*-Pyrrol-3-one 1-oxides (e.g. **9**)



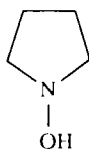
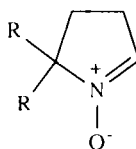
undergo cycloaddition reactions with activated dieneophiles, but only in the case of activated alkenes could the bicyclic adducts, exemplified by **10**



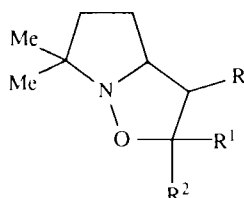
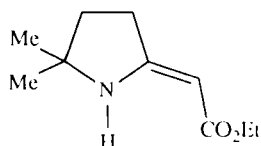
and **11**, be isolated [76JCS(P1)2259]. Dimethyl acetylenedicarboxylate gave the pyridine **13**, probably via **12** as indicated. Very surprisingly, the same pyridine was obtained from dimethyl maleate, as dimethyl fumarate gave **11**. The oxide **9** with phenylmagnesium bromide gave 1,3-dihydroxy-2,3,4,5-tetraphenyl-4-pyrroline (30JA1590).

### C. REDUCED 1-HYDROXYPYRROLES

1-Hydroxypyrrolidine (**14**), a colorless oil, is readily obtained from 1-ethylpyrrolidine by conversion to the 1-oxide and then heating to split out ethylene. Direct oxidation of pyrrolidine by performic acid gave only a 1% conversion (59CB1748). Oxidation of **14** with mercuric oxide now gave 1-pyrroline 1-oxide **15** as a distillable liquid. Phenylmagnesium bromide added across the dipolarophilic system of **15** yielded 1-hydroxy-2-

**14****15** R = H**16** R = Me

phenylpyrrolidine (59CB1748). This reaction has been greatly developed (next section) to make many 1-hydroxypyrrolidine-derived radicals. The addition of ethyl acrylate to 5,5-dimethyl-1-pyrroline 1-oxide (**16**) at room temperature gave **17** quantitatively, but at 100°, **18** was obtained [63JCS4693; 66JCS(C)1338], also in quantitative yield; the mode of addition depends on the activated diene [66JCS(C)1338]. Diethyl malonate combined with **16** to give **19**, which on heating lost carbon dioxide, yielding **20** [67JCS(C)1683].

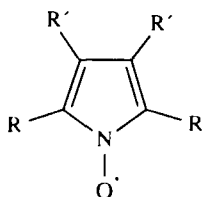
**17** R = R<sup>1</sup> = H, R<sup>2</sup> = CO<sub>2</sub>Et**18** R = R<sup>2</sup> = H, R<sup>1</sup> = CO<sub>2</sub>Et**19** R = CO<sub>2</sub>Et, R<sup>1</sup> + R<sup>2</sup> = O**20**



## D. RADICALS

1. *Aromatic Radicals*

The most investigated radicals based on 1-hydroxypyrrole have all been highly substituted so that decomposition and polymerization have been inhibited. The parent 1-oxypyrrole radical has not yet been prepared, but splitting parameters have been estimated (70MI1). 1-Hydroxytetraphenylpyrrole with lead dioxide (68BSF4679), or on cathodic oxidation (70BCF215; 73TL1863), gave the yellow radical **21**, the association and dimerization of which has been measured by electron spin resonance (ESR) and ultraviolet spectroscopy (70BCF215). It exists as the nonradical dimer in the solid state. The radical **22** is stable as the monomer, but **23** and **24** formed dimers showing the importance of steric hindrance in preventing association (73TL1863). The radical **22** has been prepared from the corresponding 1-hydroxypyrrole by lead dioxide oxidation and obtained as a blue compound which was fully characterized (70BSF4330); reduction with zinc and acetic acid gave back the 1-hydroxypyrrole. The spin densities for these radicals calculated by Hückel molecular orbital and MacLachlan methods were in agreement with the observed ESR spectra (77MI1). Spin-labelled polystyrene has been prepared from **22** (80MI2).



**21** R = R' = Ph

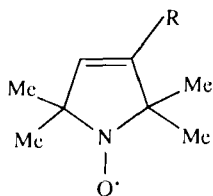
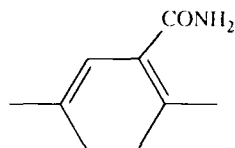
**22** R = *t*-Bu, R' = CO<sub>2</sub>Et

**23** R = Me, R' = CO<sub>2</sub>Et

**24** R = CO<sub>2</sub>Me, R' = CO<sub>2</sub>Et

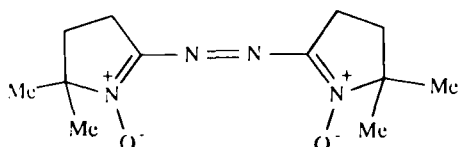
2. *Unsaturated Radicals*

A number of 2,5-dihydropyrrole 1-oxyls have been prepared (78CRV37; 83BBA229), often by oxidation of the corresponding 1-hydroxypyrroles with hydrogen peroxide and sodium tungstate (65T491), and all are fully substituted at the 2 and 5 positions. They have been used mostly as spin labels. For example, the acid **25** (65T491), prepared by alkaline hydrolysis of **29** and which with diazomethane gives the corresponding ester-radical, has been converted to the mixed anhydride **26**, and the reaction of this with polylysine has been examined (67BBA583). Also, compounds **27** and **28** were used to investigate the active center of aconitase (83BBA229). Photolysis of the amide **29** gave nitric oxide and diene **30** in high yield

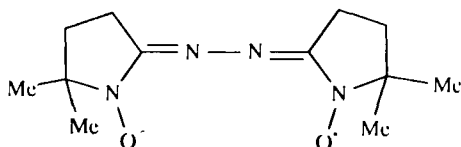
25  $R = \text{CO}_2\text{H}$ 26  $R = \text{COOCO}_2\text{Et}$ 27  $R = \text{COCH}_2\text{Br}$ 28  $R = o\text{-C}_6\text{H}_4\text{CHO}$ 29  $R = \text{CONH}_2$ 

30

(71JOC209). The blue radical-anion **32** is stable for months in the absence of air and was obtained from the 1-oxide **31** by reduction with sodium [68JCS(B)1311].



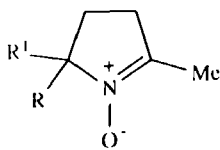
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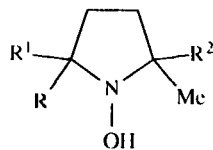
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### 3. Saturated Radicals

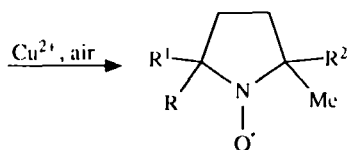
The nitroxyl radical is a stable group provided that, in general, there is no  $\alpha$ -hydrogen atom, as is the case for 2,2,5,5-tetra-substituted pyrrolidin 1-oxyls (e.g. **35**). Many compounds of this type have been synthesized, and the usual route starts from a nitron (e.g. **33**) which, with a suitable Grignard reagent or alkyl lithium, yields the 1-hydroxypyrrolidine (e.g. **34**). Oxidation, often *in situ* with copper(II) and air, gives the corresponding 1-oxyl (**35**) (78CRV37; 84MI6), which incidentally is very easily re-



33

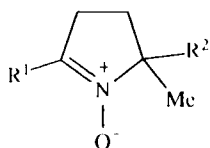
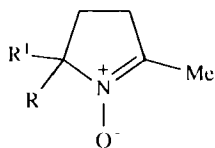
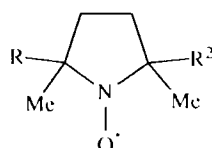


34



35

duced back to **34** by phenylhydrazine (75JOC3145). For **34**, when  $R = H$ , oxidation yields the nitron **36** ( $R' = Me$ ), while if  $R^2 = H$ , the product is **38**. These nitrones can also be converted by alkyl metals and oxidation to the corresponding 1-oxyls (cf. **35**). The alkyl metal attacks mostly from the least-hindered side, leading to a predominance of the trans isomer. If a cis isomer is needed, then the smallest alkyl group can be put into position last; in that event, for example, the nitron **37**, on successive treatment with *R*-metal, oxidation, and methyl lithium, and then oxidation, gives mainly **39**.

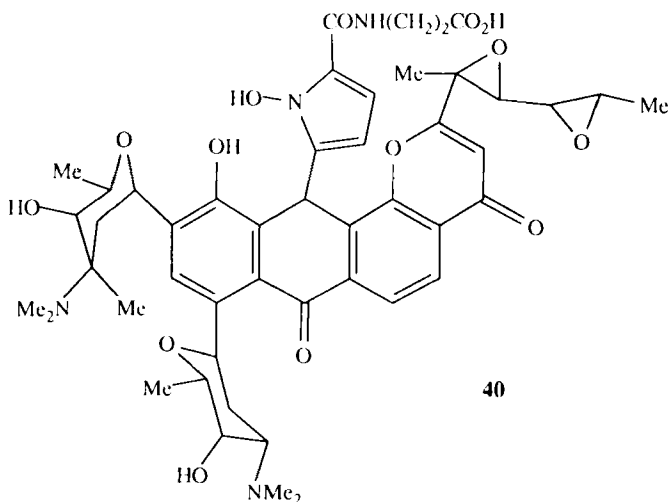
**36****38****39**

**37**  $R^1 = H$

Of the many (78CRV37) investigations of biological and other systems using pyrrolidine 1-oxyl spin labels, only a few can be mentioned here. The ESR spectra of various 1-oxyls in thiourea inclusion crystals, in model membranes, and in the presence of ascorbic acid and dihydrothreitol, which cause loss of signal due to reduction, have been examined (79BBA369), and the ESR spectra of the spin label, which is related to the interactions in the system being examined, observed. Some crown ethers and cryptands containing pyrrolidine 1-oxyl spin labels have been made, and the effects of complexation on their ESR spectra described (83JOC2647). The ESR spectra of various pyrrolidine 1-oxyls with long aliphatic chains, both saturated and unsaturated (79MI2), bearing cationic and anionic ends, have been investigated in connection with studies on detergents (82MI1); their interaction with reconstituted cytochrome oxidase where motion-restricted spectra were observed has been reported (82MI2; 86B574). A cholesterol spin label has been prepared and the nature of protein-cholesterol interactions in high-density lipoprotein examined (81JA4904). Pyrrolidine 1-oxyl spin labels have been attached to chlorophyll (78MI3) and to hemoglobin where attachment took place at more than one site (82CJC1439).

## E. NATURAL OCCURRENCE

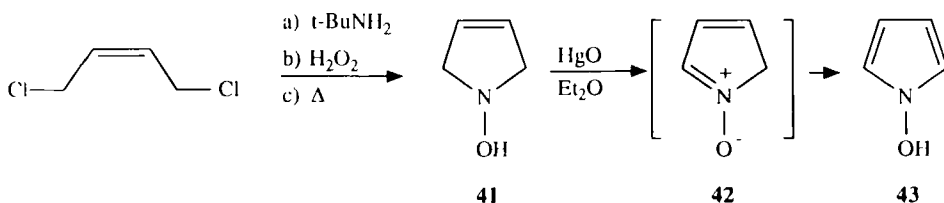
The antibiotic chromoxymycin has been identified as the 1-hydroxypyrrole **40**, mainly from a detailed study of its  $^1H$ - and  $^{13}C$ -NMR spectra (85TL3273).



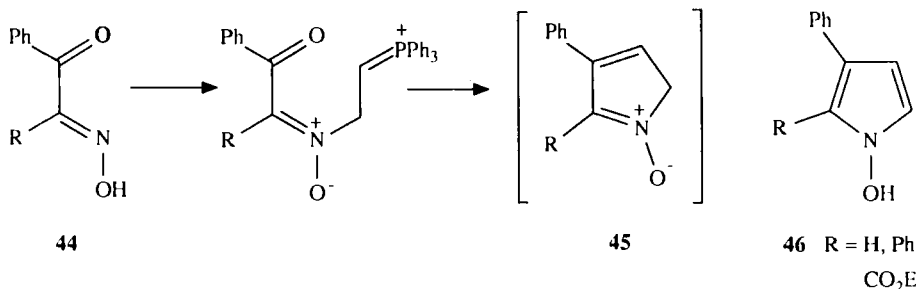
## F. SYNTHETIC METHODS

Most of the synthetic methods described here have much scope for development.

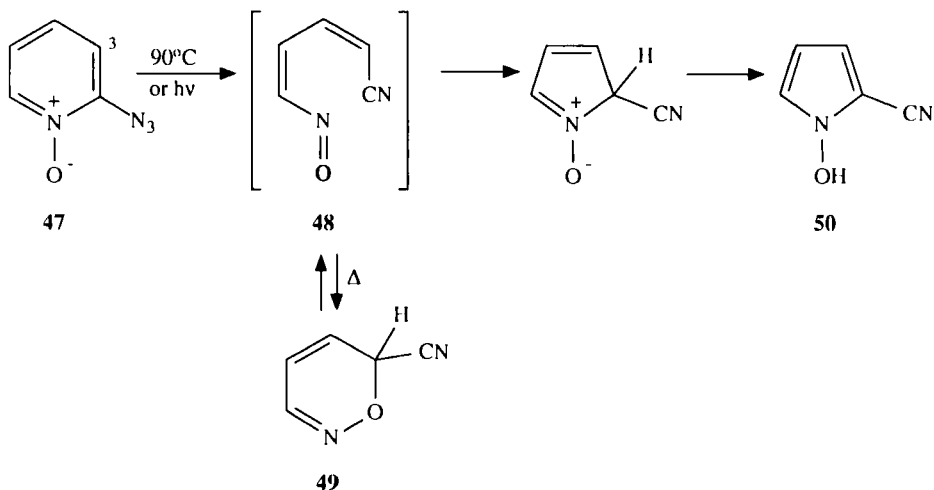
- (1) 1-Hydroxypyrrole itself (**43**) has only been obtained [76ZN(B)599] so far by the room temperature mercuric oxide dehydrogenation of 1-hydroxy-3-pyrroline (**41**), prepared as outlined from Z-1,4-dichloro-2-butene. The presumed first-formed tautomer **42** was not detected.



- (2) Three 1-hydroxy-3-phenylpyrroles (**46**) were formed (72JOC1561) in 26–44% yields, instead of the anticipated 6*H*-oxazines, when the corresponding *E*-oximes (**44**) were treated successively with one equivalent of sodium hydride in dimethylformamide (DMF) followed by triphenylvinylphosphonium bromide; *Z*-benzil oxime gave no pyrrole. The cyclization probably proceeds via cyclization to the *N*-oxide **45** and tautomerism to the 1-hydroxypyrrole.

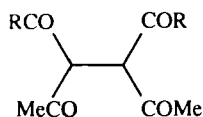
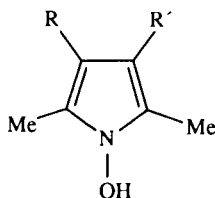
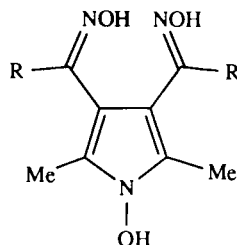


- (3) The 90° thermolysis of 2-azidopyridine *N*-oxide (47) (76JA1478) gave 2-cyano-1-hydroxypyrrole 50 in 90% yield. The low temperature needed suggested that a concerted nitrogen loss and ring opening to 48, but not nitrene formation, led to the pyrrole. More detailed studies, also on substituted derivatives, showed (81CC36) that photolysis of the azide (350 nm, in toluene) at room temperature gave the oxazine 49, which polymerized on standing, but which isomerized to the 1-hydroxypyrrole in hot toluene. The stepwise conversion of the azide via the oxazine to the 1-hydroxypyrrole in hot benzene was followed by thin-layer chromatography and <sup>1</sup>H-NMR, but the postulated intermediate 48 could not be detected or trapped. If a 3-substituent was present in the pyridine 47, rearrangement of the resulting oxazine cannot occur. The oxazine is probably the kinetically preferred product from the open-chain intermediate, and the pyrrole is the more stable one.

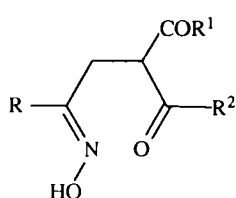
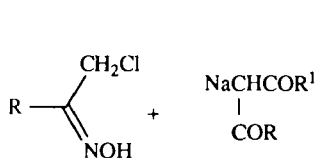
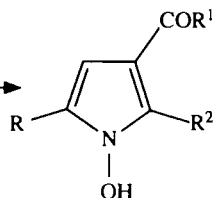
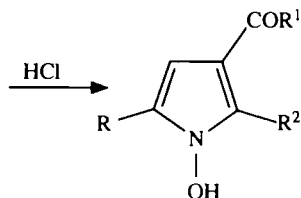
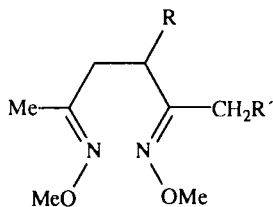


- (4) Knorr (1886LA290) first made 1-hydroxy-2,5-dimethylpyrrole by treating diethyl  $\alpha\beta$ -diacetylsuccinate (51) with hydroxylamine when a

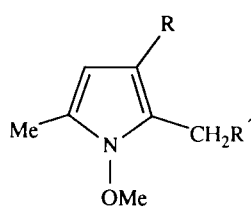
mixture of **53** and **54** was obtained; heating **53** gave **54**, and hydrolysis and decarboxylation of **54** gave the pyrrole **55**. Diethyl 1-hydroxy-2,5-di-*t*-butylpyrrole-3,4-dicarboxylate has been obtained essentially by Knorr's synthesis (70BSF4330). These reactions are similar to the hydroxylamine hydrochloride/sodium carbonate conversion of 3,4-diacetyl-2,5-hexandione (64G393) to **56** ( $R = \text{Me}$ ), and of 3,4-dibenzoyl-2,5-hexandione (84LA199) to a mixture of **56** ( $R = \text{Ph}$ ) and 3-benzoyl-1-hydroxy-2-methyl-5-phenylpyrrole (**58**,  $R = R^1 = \text{Ph}$ ,  $R^2 = \text{Me}$ ).

**51**  $R = \text{OEt}$ **52**  $R = \text{Me}$ **53**  $R = \text{CO}_2\text{Me}$   $R' = \text{CO}_2\text{H}$ **54**  $R = \text{CO}_2\text{Me}$   $R' = \text{H}$ **55**  $R = R' = \text{H}$ **56**

$\alpha$ -Bromo- [60AC(R)1627] and  $\alpha$ -chloro-ketone oximes with the sodium derivatives of 1,3-diketones or 1,3-ketoesters yield the expected

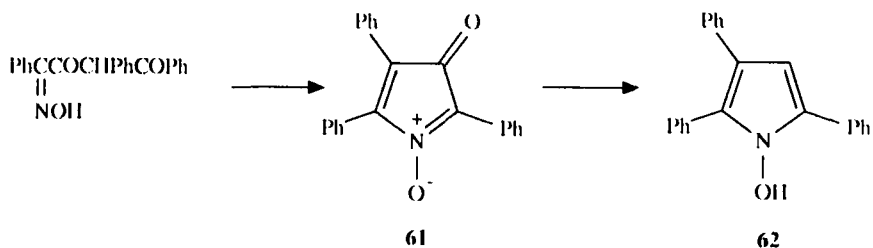
**57****58****59**  $\underline{Z}$ ,  $\underline{Z}$ ,  $R = \text{PhCH}_2$ ,  $R' = \text{H}$ 

and  $\underline{E}$ ,  $\underline{E}$ ,  $R = \text{H}$ ,  $R' = \text{PhCH}_2$

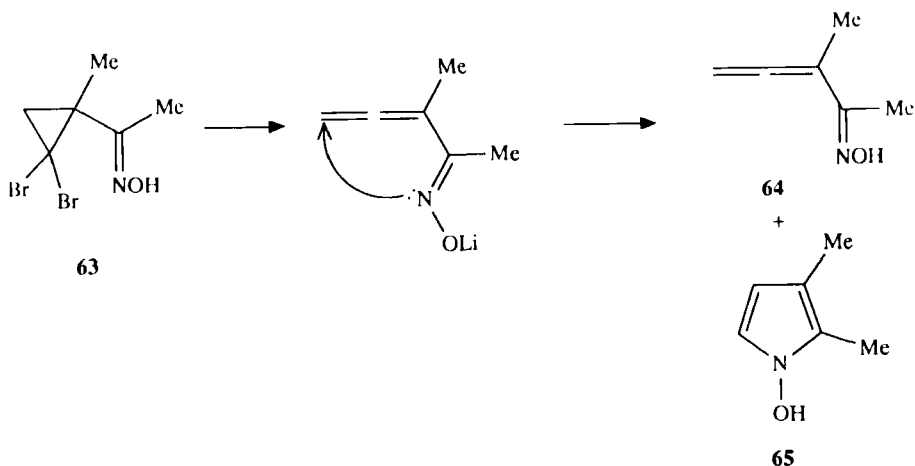
**60**

products **57** which, on in situ treatment with gaseous hydrogen chloride, yield the 1-hydroxypyrroles **58** ( $R = \text{Me, Ph}$ ;  $R^1 = \text{Me, Ph, OEt}$ ;  $R^2 = \text{Me}$ ). The  $\alpha$ -ketoester **57** ( $R = R^1 = \text{Ph}$ ,  $R^2 = \text{CO}_2\text{Me}$ ) also gave (79JHC203) the corresponding pyrrole. Similar cyclizations of the bis-*O*-methyl oximes (**59**) gave (83S590) the corresponding 1-methoxypyrroles **60**.

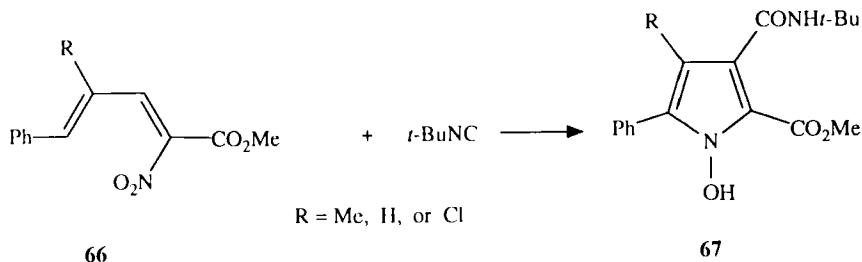
1,3,4-Triphenyl-1,2,4-butanetrione oxime in chloroform with hydrogen chloride cyclized in 70–75% yield to the purple 2,4,5-triphenyl-3*H*-pyrrol-3-one 1-oxide (**61**) (30JA1590), along with an isoxazoline derivative. The pyrrolone was reduced by lithium aluminum hydride in ether [76JCS(P1)2259] to 1-hydroxy-2,3,5-triphenylpyrrole **62**.



- (5) 1-Chloro-2,3,4,5-tetrakis(trifluoromethylthio)pyrrole with potassium cyanide is stated, on the basis of spectral evidence, to give the corresponding 1-(*O*-cyano)pyrrole (85CB4588).
- (6) Treatment of the oxime **63** with methyl lithium at  $-20^\circ$  gave 2,3-dimethyl-1-hydroxypyrrole (**65**) in 50% yield, along with 20% of the allene oxime (**64**), which is the product isolated from this type of reaction when the cyclopropene contains additional alkyl groups (80TL2893).



- (7) Heating the methyl 2-nitro-5-phenyl-2,4-pentadienoates (**66**) with *t*-butylisocyanide gave the corresponding 1-hydroxypyrroles (**67**) (83JOC3639), the mechanism probably being similar to that suggested for the formation of 1-hydroxyindole **49** (see Section III,G).

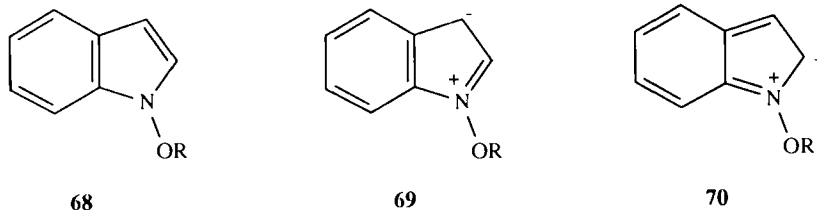


### III. 1-Hydroxyindoles

#### A. STRUCTURE AND SPECTRA

##### 1. Molecular Dimensions and Tautomerism

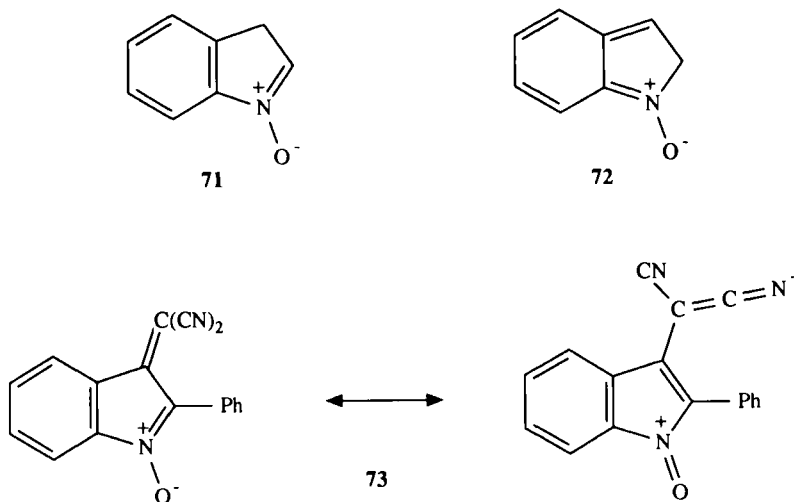
Molecular dimensions are not available for 1-hydroxyindole (**68**, R = H), for which resonance forms **69** and **70** can be written. The electronegativity of the oxygen atom would be expected to reduce the importance of these contributors, compared to N-nonhydroxylated analogues, and so



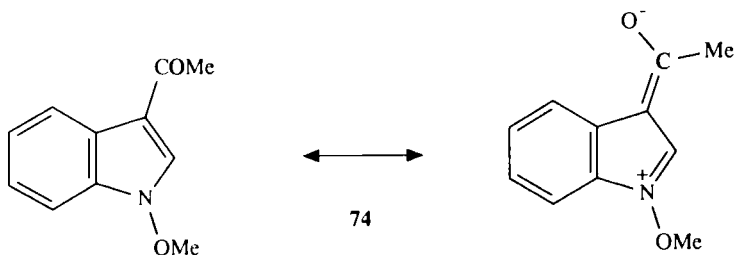
increases the tendency of the nitrogen to adopt an  $sp^2$  configuration with the oxygen atom away from the ring plane. The X-ray crystal structures of five *N,N'*-dialkylanilines show that the bonds from the nitrogen are coplanar, while for an *N*-alkylphenylhydroxylamine, the nitrogen adopts pyramidal bonding [for references see 83JCS(P2)497]. This suggests that the oxygen atom assists the nitrogen atom to retain pyramidity. Tautomerism to **71** and **72** could also occur where a planar nitrogen would be expected, and in some solvents, ( $^1\text{H}$ -NMR studies following), tautomer **71** has been detected. An X-ray crystal structure determination (87M369) for



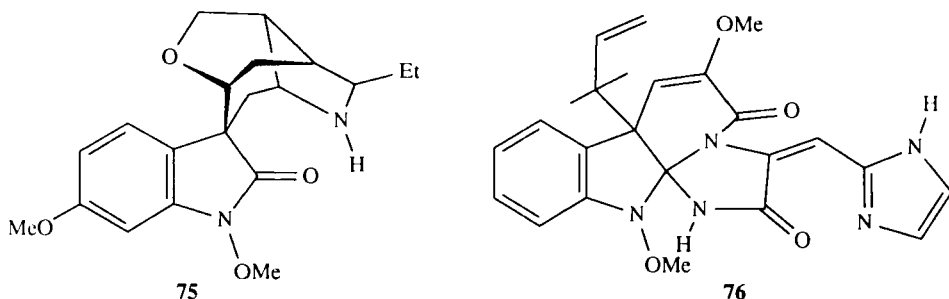
**73** with  $R = 0.053$ , shows that the N—O bond makes an angle of  $0.7^\circ$  with the indole ring plane and an angle of  $0.3^\circ$  with the heterocyclic ring plane. Also, the sum of the bond angles at the nitrogen atom was  $360^\circ$ , as is also the case for 1-hydroxy-2-phenylindole in a complex with 4-(4-dimethylaminophenyl)azopyridine (83G153). The N—2C bond length in **73** [ $1.336(3) \text{ \AA}$ ] was experimentally the same as the corresponding bond [ $1.340(5) \text{ \AA}$ ] in pyridine (76M11). The 2C—3C bond length [ $1.445(3) \text{ \AA}$ ] was significantly longer than that in normal indoles [ $1.359(5) \text{ \AA}$ ] [83JCS(P2)497], so it is clear that substantial electron delocalization occurs as indicated; the phenyl group lies at  $78^\circ$  to the indole ring plane and is little involved.



The X-ray crystal structure [83JCS(P2)497] of 1-benzoyloxyindole (**68**,  $R = \text{COPh}$ ), with  $R = 0.043$ , showed that the nitrogen atom was distinctly pyramidal, the oxygen atom attached to the ring being  $0.345 \text{ \AA}$  away from the best ring plane. The sum of the angles around the nitrogen atom was  $355^\circ$ , substantially greater than that ( $329^\circ$ ) of an alkylphenylhydroxylamine [74JCS(P2)1210]. A comparison of these bond lengths with those of other indoles shows the benzoyloxy group exerts a small but significant electron-withdrawing effect on the nitrogen atom [83JCS(P2)497]. Nothing is known concerning the rotation barrier about the N—O bond [cf. 78JCS(P2)707]. The crystal structure of 3-acetyl-1-methoxyindole, also determined by X-ray diffraction ( $R = 0.054$ ) [80AX(B)3125], showed that the bonds from the nitrogen atom were almost coplanar, and that the acetyl group was almost coplanar with the heterocyclic ring and in the conformation shown **74**. The N—O bond length ( $1.394 \text{ \AA}$ ) was very similar to



that of **68** ( $R = \text{PhCO}$ ), but the lengths of the  $\text{N}-2\text{C}$  and  $2\text{C}-3\text{C}$  bonds were shorter and longer, respectively, than the corresponding bonds in indole-3-acetic acid, indicating that electron delocalization involving the carbonyl group is strong and must contribute to the planarity of the bonds from the nitrogen atom. A planar indolic nitrogen atom has been reported (62AX301) for gelsemicine (**75**), but this conclusion is not certain [83JCS(P2)497] because of the high  $R$  factor value (0.16). The structure of oxaline (**76**) was determined by X-ray crystallography (74CC1021). A planar arrangement of the oxygen and the ring was assumed for calculating the most favorable conformations in 1-acetoxy- and 1-methoxy-indole for  $\text{C}-\text{H}$  coupling constant calculations (87M15).



## 2. Ultraviolet Absorption Spectra

The ultraviolet absorption spectra of most 1-hydroxy-, 1-acyloxy-, and 1-alkoxyindoles are quite similar to those of the corresponding indoles; representative examples are listed in Table II. In general, they show a small shift towards the visible, and this is accentuated in the 1-hydroxyindoles on the addition of alkali when the proton can be removed. The UV spectrum reported (67BSF1296) for 1-hydroxyindole is certainly that of a polymer, for it shows no absorption at  $\sim 280$  nm, which is characteristic of these compounds and of 2,3,3-trimethyl-3*H*-indolenine 1-oxide, a model for the 3*H*-tautomer (Table II).

TABLE II  
THE ULTRAVIOLET SPECTRA OF 1-OXYGENATED INDOLES

Substituents	Solvent	$\lambda_{\max}$ nm ( $10^{-4}\epsilon$ )	References
1-HO-2-Me	MeOH	223 (3.49), 284 (0.80)	67BSF1296; 7OUP1
1-HO-2-Ph	MeOH	224 (2.40), 305 (2.30)	67BSF1296; 7OUP1
	MeOH <sup>a</sup>	316 (1.62)	
1-HO-3-CHO	MeOH	213 (0.74), 245 (0.36), 255 (0.31), 308 (0.29), 350 (2.22)	78JCS(P1)1117
1-HO-3-COCO <sub>2</sub> H	MeOH	222 (2.09), 245 (0.71), 255 (0.68), 313 (0.53), 395 (0.20)	78JCS(P1)1117
1-HO-3-CN-2-Me	EtOH <sup>b</sup>	229 (1.85), 290 (1.05)	70JCS(C)1916
1-HO-2-CO <sub>2</sub> Me	MeOH	225 (2.16), 293 (1.74)	68JCS(C)504
	MeOH <sup>a</sup>	301 (1.00), 310 (1.33), 358 (0.27)	68JCS(C)504
2,3,3-Me <sub>3</sub> 1-oxide	Hexane	203 (1.90), 287 (0.60)	67BSF1296
1-MeO	MeOH	218 (2.34), 270 (0.41), 288 infl (0.34), 296 (0.25)	78JCS(P1)1117
1-MeO-2-CH <sub>2</sub> CN	EtOH	218 (2.63), 270 (0.50), 286 (0.40), 297 (0.38)	70ABC1590
1-MeO-3-CH <sub>2</sub> CH <sub>2</sub> CN			
	MeOH	223 (3.09), 278 (0.46), 291 (0.48)	65LA212
1-MeO-3-CHO	MeOH	214 (1.55), 245 (1.07), 350 (1.04)	78JCS(P1)1117
1-MeO-2-CO <sub>2</sub> Me	MeOH	226 (2.20), 291 (1.98),	68JCS(C)504
1-MeO-3-COCO <sub>2</sub> Me	MeOH	212 (1.40), 253 (0.49), 310 (0.52)	78JCS(P1)1117

<sup>a</sup> Basified.

<sup>b</sup> Containing 5% H<sub>2</sub>O.

### 3. Infrared Spectra

The infrared spectra of over 20 1-oxygenated indoles have been collected [79MI1; see also 78JCS(P1)1117]. In the 1-hydroxy compounds, the positions of the HO bands are sensitive to both the conditions of measurement and to the other substituents present, and hydrogen bonding may or may not be observed. For example, 1-hydroxy-2-methylindole in nujol shows a sharp peak at  $3415\text{ cm}^{-1}$  and a broad band between  $2230$  and  $3385\text{ cm}^{-1}$ , while in carbon tetrachloride, the corresponding bands for nonbonded and bonded hydroxyl appear  $3510$  and  $2300\text{--}3450\text{ cm}^{-1}$ . The range for unbonded and bonded hydroxyl appears to be between  $3100$  and  $3510\text{ cm}^{-1}$  and (broad absorption) between  $2230$  and  $3450\text{ cm}^{-1}$ , respectively.

A useful diagnostic criterion for 1-acetyloxy groups is the very high carbonyl frequency, usually about  $1810\text{ cm}^{-1}$ , but occasionally up to  $1825\text{ cm}^{-1}$  [78JCS(P1)1117; 87JHC1145]. Lower values ( $1760\text{--}1783\text{ cm}^{-1}$ ) are observed for 1-arylcarbonyloxyindoles [78JCS(P1)1117]. A 1-methoxy group may be associated with an absorption at  $\sim 1520\text{ cm}^{-1}$ .

4.  $^1\text{H-NMR}$  Spectra

The instability of 1-hydroxyindole (**77**,  $\text{R} = \text{H}$ ) has precluded a full  $^1\text{H-NMR}$  analysis. The data for a carbon tetrachloride solution (Table IV) are totally consistent with the presence of this compound, and in deuteriochloroform solution, the spectrum was similar, but the peak integration ratios and the appearance of a resonance at  $\sim 3$  ppm suggested that up to 20% of 3*H*-indole 1-oxide (**79**) might be present [78JCS(P1)1117]. The spectra of the much more stable 1-hydroxy-2-methylindole in various solvents (Table III) showed that the equilibrium position for the hydroxyl (**78**) and the 1-oxide (**80**) tautomers was highly solvent-dependent [70JCS(C)1067]. 1-Hydroxy-2-phenylindole was similar, showing only the indole tautomer in DMF and the 3*H*-indole 1-oxide tautomer in methanol (81CPB1827). The  $^1\text{H-NMR}$  spectra of 1-hydroxyindole-2-carboxylic acid

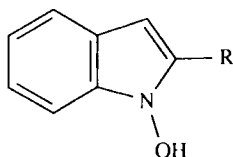
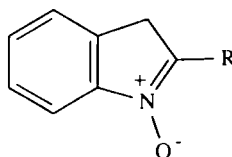
77  $\text{R} = \text{H}$ 78  $\text{R} = \text{Me}$ 79  $\text{R} = \text{H}$ 80  $\text{R} = \text{Me}$ 

TABLE III  
THE  $^1\text{H-NMR}$  SPECTRA OF 1-HYDROXY-2-METHYLINDOLE (**78**)  
AND 2-METHYL-3*H*-INDOLE 1-OXIDE (**80**) IN  $\delta$  (J IN HERTZ)  
FROM INTERNAL  $\text{Me}_4\text{Si}$  [70JCS(C)1067]

Solvents	1 <i>H</i> -indole				3 <i>H</i> -indole		
	1-HO <sup>a</sup>	2-Me	3-H	%	2-Me	3-CH <sub>2</sub>	%
$\text{C}_5\text{D}_5\text{N}$	8.71	2.50 <sup>b</sup>	6.31	100	—	—	0
$\text{CD}_3\text{CN}$	8.30 <sup>c</sup>	2.40 <sup>b</sup>	6.06	100	—	—	0
$\text{CH}_3\text{NO}_2$	8.25 <sup>c</sup>	2.39 <sup>b</sup>	6.04 <sup>d</sup>	76	2.05	2.39	24
$\text{CDCl}_3$	9.75	2.35	5.81 <sup>d</sup>	60	1.77	3.15 <sup>d</sup>	40
$\text{CCl}_4$	8.94	2.31	5.77 <sup>d</sup>	67	1.30	2.71 <sup>d</sup>	33
$\text{CCl}_4\text{-PhOH}$ (27%)	— <sup>e</sup>	2.26	—	62.5	1.46	2.72	37.5
$\text{CCl}_4\text{-PhOH}$ (90%)	— <sup>e</sup>	2.22	— <sup>e</sup>	55	1.71	2.8 <sup>d</sup>	45
PhOH	—	—	—	0	2.13	2.80	100

<sup>a</sup> Immediate exchange with  $\text{D}_2\text{O}$ .

<sup>b</sup> J 1.2.

<sup>c</sup> Very broad.

<sup>d</sup> Exchanges with  $\text{D}_2\text{O}$ .

<sup>e</sup> Obscured by solvent.

TABLE IV  
<sup>1</sup>H-NMR SPECTRA OF SELECTED INDOLES, IN CDCl<sub>3</sub> UNLESS NOTED [δ(J IN HERTZ)] FROM INTERNAL Me<sub>4</sub>Si

Substituents	Proton assignments							References
	1	2	3	4	5	6	7	
1-HO <sup>a</sup>	7.75 <sup>b</sup>	—	6.02 <sup>c</sup> J3.3	—	6.7	7.5 <sup>d</sup>	—	78JCS(P1)1117
1-HO-2-Me see Table III								
1-HO-3-CHO <sup>c</sup>	—	8.28	10.22 <sup>f</sup>	8.1m	7.1	—	7.6 <sup>d</sup>	78JCS(P1)1117
1-HO-2-CO <sub>2</sub> Me	10.03 <sup>b</sup>	3.88 <sup>g</sup>	6.98	6.95	—	—	7.7 <sup>d</sup>	68JCS(C)504
1-HO-3-CO <sub>2</sub> H <sup>h</sup>	—	7.90	—	8.13m	7.08	—	7.68 <sup>d</sup>	84JCR(M)1301
1-AcO <sup>i</sup>	1.98 <sup>g</sup>	6.966	6.329	7.189	7.037	7.127	7.116	87MI5
1-MeO	3.90 <sup>g</sup>	J <sub>2,3</sub> 3.46, J <sub>4,5</sub> 8.01, J <sub>4,6</sub> 1.06, J <sub>4,7</sub> 0.88, J <sub>5,6</sub> 6.45, J <sub>5,7</sub> 1.65, J <sub>6,7</sub> 8.02						87MI5
		7.14	6.30	7.55	7.07	7.20	7.39	
1-MeO-2-CO <sub>2</sub> Me	4.20 <sup>g</sup>	J <sub>2,3</sub> 3.3, J <sub>2,6</sub> 0.26, J <sub>3,7</sub> 0.89, J <sub>4,5</sub> 8.07, J <sub>4,6</sub> 1.12, J <sub>4,7</sub> 0.75, J <sub>5,6</sub> 7.06, J <sub>5,7</sub> 1.03, J <sub>6,7</sub> 8.20						
1-MeO-3-CHO	4.08 <sup>g</sup>	2.93 <sup>g</sup>	7.12	3.05	—	—	3.75 <sup>d</sup>	68JCS(C)504
		7.79	9.37 <sup>f</sup>	8.26	7.10	—	7.57 <sup>d</sup>	78JCS(P1)1117

<sup>a</sup> Solvent: CCl<sub>4</sub>.

<sup>b</sup> Exchanges rapidly with D<sub>2</sub>O.

<sup>c</sup> Exchanges slowly with D<sub>2</sub>O.

<sup>d</sup> Unassigned protons.

<sup>e</sup> Solvent (CD<sub>3</sub>)<sub>2</sub>SO.

<sup>f</sup> CHO.

<sup>g</sup> CH<sub>3</sub>.

<sup>h</sup> Solvent: CD<sub>3</sub>OD.

<sup>i</sup> 500 MHz spectrum.

(84CPB3678) and the ester (Table IV) show that these compounds exist entirely as the hydrogen-bonded 1-hydroxy tautomers, but in contrast, 3-bromo-1-hydroxyindole-2-carboxylic acid appears to favor the 3*H*-indole 1-oxide form [68JCS(C)504]. Only the 1-hydroxy tautomer was observed in a number of cases in deuteriochloroform and in hexadeuterio-dimethylsulfoxide solutions (83JOC3639).

The  $^1\text{H}$ -NMR spectra of 1-acetoxy- and 1-methoxyindoles have been very carefully analyzed (Table IV) and subject to intensive theoretical studies (87MI5). Long-range coupling between the 3- and 7-protons, detected earlier in substituted derivatives [78JCS(P1)1117], and between other protons has been established and is similar to that observed (87MI5) in similar 1-substituted indoles. The spectra of a selected number of 1-hydroxyindoles are given in Table IV, and many further examples have been tabulated [78JCS(P1)1117; 79MI1]. The spectrum of 1-methoxyindole was hardly affected by  $[\text{Eu}(\text{fod})_3]$  [78JCS(P1)1117].

### 5. $^{13}\text{C}$ -NMR Spectra

The  $^{13}\text{C}$ -NMR spectra for several indoles and 1-hydroxy-, 1-acetoxy-, and 1-methoxyindoles have been very carefully measured, and selected data is presented in Table V. In the oxygenated compounds, which have quite similar spectra, the 3-carbon atom moves significantly upfield, as does the 7-carbon atom, but to a smaller extent. Detailed correlations between the various substituents and the chemical shifts and coupling

TABLE V  
 $^{13}\text{C}$ -NMR SPECTRA FOR 1-SUBSTITUTED INDOLES MEASURED  
IN  $\text{CDCl}_3$  AND RECORDED IN PPM FROM  $\text{Me}_4\text{Si}$  (76T2625)

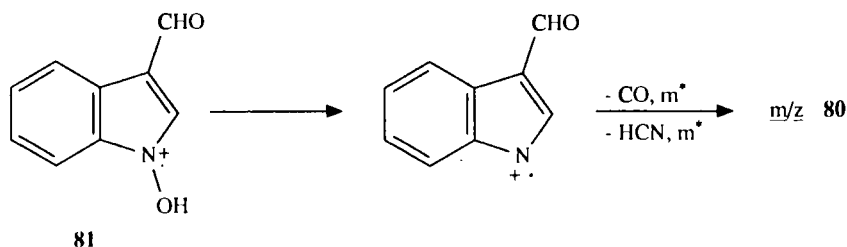
Carbon atom	1-Substituent			
	H	OH	OMe	OAc
2	124.09	125.17	122.73	124.76
3	102.12	96.65	97.86	99.38
4	120.42	120.76	121.00	120.81
5	119.45	119.27	119.78	120.27
6	120.60	121.71	122.10	122.54
7	110.94	108.46	108.03	107.91
8	127.70	?	124.13	124.18
9	135.69	?	131.68	133.36
$\text{CH}_3$	—	—	65.49	17.22
CO	—	—	—	168.16

constants also have been made. The spectrum for a 1-methoxyindoline has been measured (76T2625).

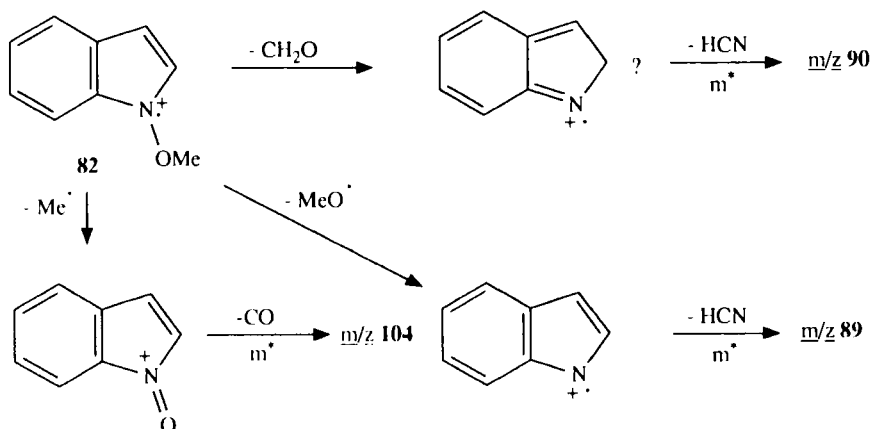
## 6. Mass Spectra

Data on the mass spectra of 1-oxygenated indoles is rather superficial, and high-resolution data is almost entirely lacking. However, it is clear that the bonds on either side of the oxygen atom are easily fragmented, and the loss of the whole 1-substituent is a common feature. The mass spectrum of 1-hydroxyindole has not been obtained, because of its instability, but the high-resolution spectrum [70JCS(C)1067] of the 2-methyl derivative (**78**) shows the molecular ion as the base peak and a peak (50%) corresponding to the loss of OH. Fragments corresponding to the loss of HCN and HCO must arise through rearrangements. A number of other 1-hydroxyindoles show the molecular ion and peaks due to the loss of the oxygen atom (83JOC3639).

1-Hydroxyindole-3-carbaldehyde loses OH from the molecular ion (**81**), which is the base peak (78MI2), while the corresponding acid loses O

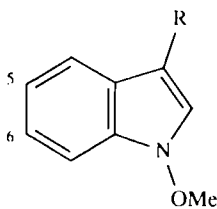


(80%), CO<sub>2</sub> (79%), and CO<sub>2</sub>H + OH to give the base peak [84JCR(M)1301]. 1-Methoxyindole loses CH<sub>2</sub>O from the molecular ion (**82**), possibly by a cyclic mechanism [the 4-nitro derivative was similar



(81CPB726)] to give the base peak, which subsequently loses HCN. There is a substantial peak (31%) corresponding to the loss of  $\text{OCH}_3$ , but no supporting metastable peak was found. Loss of a methyl group from the molecular ion was confirmed by a metastable transition. In the case of 6-chloro-1-ethoxyindole, metastable transitions corresponding to the loss of ethylene and the ethoxy group from the molecular ion were found (78MI2).

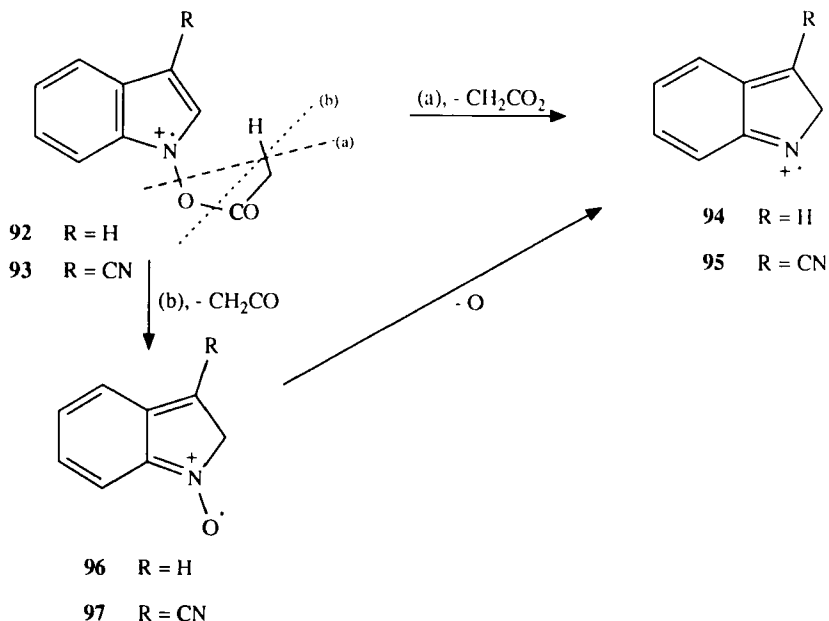
The mass spectra of some substituted 1-methoxyindoles have been investigated [84JCR(M)1301]. Of these, the 3-methyl ester (**83**), the 3-cyano (**84**), and the 3-acetonitrile (**85**) derivatives of 1-methoxyindole all show molecular ions (33–80%) and the loss of Me (8–100%) and MeO (16–100%). The ester and the acetonitrile also show the loss of the 3-substituent from the molecular ion. 1-Methoxyindole-3-carboxylic acid (**86**) similarly shows the loss of Me (18%) and  $\text{CO}_2\text{H}$  (13%) from the molecular ion, and the loss of  $\text{CH}_2\text{O}$  is significant (18%). However, the base peak corresponds to the loss of  $\text{C}_2\text{H}_3\text{O}_2$ , which could correspond to  $\text{CO} + \text{MeO}$ ,  $\text{CO}_2\text{H} + \text{CH}_2$ , or  $\text{H} + \text{CO} + \text{CH}_2\text{O}$ . The corresponding 3-acrylic acid (**87**) first loses  $\text{CH}_2\text{O}$  (78MI2), while the aldehyde (**88**) loses either a hydrogen atom, followed by Me and CO from the molecular ion (100%), or Me then CO. 1-Methoxy-*N,N*-dimethyltryptamine (**89**) either loses the MeO group or the  $\text{Me}_2\text{N}=\text{CH}_2$  ion, which gives the base peak (78MI2). The base peaks from 6-chloro-1-methoxygramine (**90**) [78JCS(P1)1117] and from 1,5-dimethoxygramine (**91**) (67AJC1737) show first the loss of  $\text{Me}_2\text{N}$  from the molecular ions and subsequently the loss of MeO.

	R
	<b>83</b> $\text{CO}_2\text{Me}$
	<b>84</b> CN
	<b>85</b> $\text{CH}_2\text{CN}$
	<b>86</b> $\text{CO}_2\text{H}$
	<b>87</b> $\text{CH}=\text{CHCO}_2\text{H}$
	<b>88</b> CHO
	<b>89</b> $(\text{CH}_2)_2\text{NMe}_2$
	<b>90</b> $\text{CH}_2\text{NMe}_2$ , 6-Cl
	<b>91</b> $\text{CH}_2\text{NMe}_2$ , 5-MeO

1-Methoxyindoles unsubstituted in the five-membered ring give strong molecular ions, which lose MeO or  $\text{CH}_2\text{O}$ . If this ring is substituted, loss of the substituent or fragmentation of the substituent may take place first.



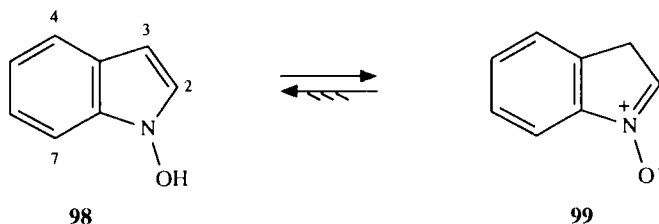
The fragmentation of 1-acetyloxyindole [78JCS(P1)1117], which gives a large (50%) molecular ion (**92**), takes place in two ways (79MI1). The base peak was formed by breaking the N—O bond (route a) with the loss of  $\text{CH}_2\text{CO}_2$  to give **94**, but the loss of ketene with scission of O—acyl bond (route b) to yield **96** was almost as important (84%); the 4-nitro derivative was similar (81CPB726). The base peak in the fragmentation of the 3-cyano derivative **93** [84JCR(M)1301] and of 1-(4-chlorobenzoyloxy)-2-methylindole [70JCS(C)1067] correspond to the acylium cation, but in the 3-cyano case the loss of ketene also gave the ion **97** (97%), which lost O to give **95**.



## B. GENERAL PROPERTIES AND CHEMICAL REACTIVITY

### 1. Hydroxyindoles

1-Hydroxyindole (**98**) is a reactive compound that has only been obtained in solution; it polymerizes to a green powder on attempted isolation [78JCS(P1)1117]. Its 4-benzyloxy derivative also could not be isolated (85JHC121), and these compounds are more difficult to handle than 1-hydroxypyrrole. A nitro (81CPB726), cyano (85JHC121), and to a lesser extent a methoxycarbonyl group (81CPB726) at the 4-position stabilizes



the molecule enormously. Cyano groups at positions 5 and 6 also stabilize the molecule, but to a much lesser extent (85JHC121). 2-Methyl-1-hydroxyindole is a relatively stable crystalline compound [70JCS(C)1067], while 1-hydroxy-2-phenylindole can be prepared using concentrated sulfuric acid, which will decompose most indoles and has been much investigated. All other substituents that have been placed at position 2, including carbonyl groups which can hydrogen-bond with the hydroxyl group, increase the stability of the molecule. 1-Hydroxyindole-2- and -3-carboxylic acids are not very stable, although the 3-aldehyde, 3-carboxamide, and 3-glyoxylic acid can be stored [78JCS(P1)1117; 84JCR(M)1301]. Substituents that make the 1-hydroxyl group more acidic, and possibly less prone to oxidation to a radical, and those that increase steric congestion near it and increase its involvement in hydrogen bonding increase the stability of the molecule as a whole. Dimerization of the 3*H*-indole 1-oxide tautomer (99) will be sterically inhibited.

The 1-hydroxy group is readily acylated, for example, with acetic anhydride and sodium hydrogen carbonate [78JCS(P1)1117] or with benzoyl chloride and pyridine or sodium hydroxide [83JCS(P2)497]. The 1-hydroxyindole is reformed on alkaline hydrolysis; many 1-hydroxyindoles have, in fact, been prepared through the hydrolysis of their O-acetyl derivatives. Alkyl halides, such as methyl iodide, in the presence of sodium methoxide give the 1-alkyloxyindoles in high yield [78JCS(P1)1117], but dealkylation to the original 1-hydroxyindole has not been achieved.

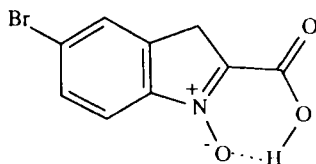
Reduction of a 1-hydroxyindole to the corresponding indole is always effected by zinc and acetic acid if sufficiently vigorous conditions are employed (1896CB646, 1896CB2062, and see 79M11, for other references) by other reagents including trimethyl phosphite (83JOC3639), titanium(III) chloride under the correct conditions (81CPB726), and by Raney nickel/sodium hypophosphite (85JHC121). It is apparently not reduced by lithium aluminum hydride or sodium borohydride, which could form salts with the hydroxyl group. Many reducing agents, including hydrogen over palladium or other catalysts, reduce 2-nitrophenylcarbonyl compounds to mixtures of indoles and 1-hydroxyindoles, but it is usually not clear if the outcome is controlled by reduction of the nitro group to an amine or

hydroxylamine prior to cyclization or reduction of the 1-hydroxyindole after cyclization of the hydroxylamine.

1-Hydroxyindole-2-carboxylic acid can be obtained [1896CB646; 68JCS(C)504] as colorless prisms, but is not easy to purify and decomposes on standing (80UP1). It decomposes at its melting point (159.5°C) to a green oil, possibly a polymer of 1-hydroxyindole, and all attempts to decarboxylate it to this last compound have failed (65MI1, 65MI2). In deuteriochloroform, this acid exists entirely as the hydrogen-bonded indole (100), but the 5-bromo derivative prefers the 3*H*-indole tautomer (101)

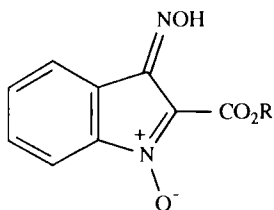


100

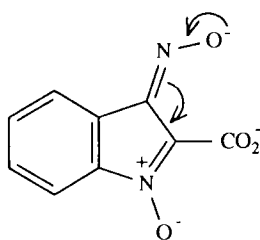


101

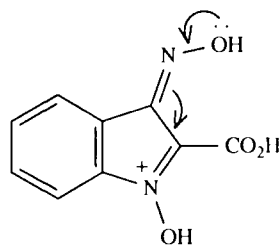
under these conditions [68JCS(C)504]. 1-Hydroxyindole-2-carboxylic acid gives blue colors with sodium hypochlorite, bromine, hydrogen peroxide, ferric chloride, and concentrated sulfuric acid and reduces hot, but not cold, Fehling's solution (1896CB646). It is oxidized by chromic acid in acetic acid to isatin with the loss of the 1-hydroxy group and by potassium permanganate to azoxybenzene-2,2'-dicarboxylic acid (1896CB646). 4-Nitroperbenzoic acid oxidizes the methyl ester to methyl isatogen-2-carboxylate (74S443). 1-Hydroxyindole-2-carboxylic acid is reduced by zinc and acetic acid (1896CB646), but not by hydrogen over platinum [67JCS(C)2466], to indole-2-carboxylic acid. The carboxyl group esterifies normally [23CB1024; 68JCS(C)504]; the 1-hydroxyl group is significantly acidic, for both it and the carboxyl group are methylated by diazomethane [68JCS(C)504], and many straightforward reactions of 1-hydroxyindole-2-carboxylic acid and its esters have been described [23CB1024; 68JCS(C)504]. The ester gives the 1-O-tetrahydropyranyl derivative with dihydropyran, and this is reduced to the corresponding 2-methanol with lithium aluminum hydride (65MI1). Both 1-hydroxyindole-2-carboxylic acid and its methyl ester are stated to give the corresponding 1-nitroindoles with nitrous acid; reduction with ammonium sulfide leads to 1-aminoindole-2-carboxylic acid (1896CB646). Nitrosation would, however, be expected to occur at position 3, giving 102. Resonance stabilization in the corresponding anion 103 and the cation 104 would then account for the stability of the compound to hot concentrated alkali, to cold concentrated sulfuric acid, and to benzoyl chloride; reduction would give 3-aminoindole-2-carboxylic acid or the ester.



102 R = H or Me

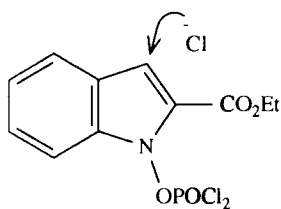


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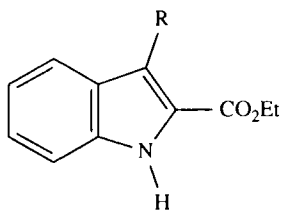


104

Ethyl 1-hydroxyindole-2-carboxylate (**100**, ester) with phosphorus oxychloride in DMF at room temperature gave only ethyl 3-chloroindole-2-carboxylate **106**, presumably via phosphorylation of the *N*-hydroxyl group (**105**), breaking the *N*—*O* bond concurrently with the chloride anion attacking at the 3-position, followed by tautomerism. Tosyl chloride and pyridine gave a mixture of **106** and **107**. Benzoyl chloride in pyridine-dimethylformamide gave some 1-*O*-benzoyl derivative, but mostly the reaction yielded **106** along with some **108**, while refluxing in acetic anhydride yielded the *O*-acetyl derivative and some **109** (84CPB3678). 3-Cyano-1-hydroxyindole-2-carboxylic acid brominated at position 5 [68JCS(C)504], while the corresponding ethyl ester with tosyl chloride in triethylamine gave **110**; none of the expected 1-tosyloxyindole was detected (72T2749).



105

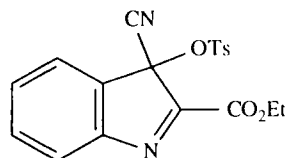


106 R = Cl

107 R = TsO

108 R = PhCOO

109 R = OAc



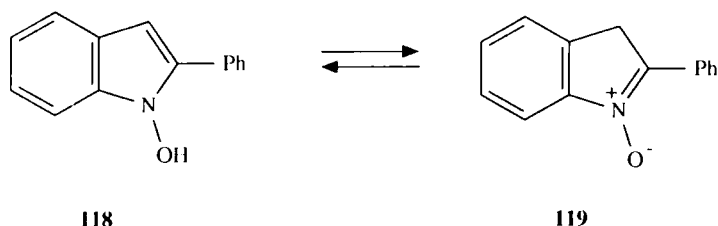
110

Attempted oxidation of 3-cyano-1-hydroxy-2-methylindole (**111**) by cold aqueous potassium permanganate or sodium dichromate in hot acetic acid caused deoxygenation to 3-cyano-2-methylindole, and photolysis of the *O*-acetyl and *O*-methoxycarbonyl derivatives gave the same product



Hydroxyindole-3-glyoxylic acid (**113**) with hydroxylamine hydrochloride yielded 3-cyano-1-hydroxyindole **115**, presumably by the cyclic process indicated (**114**), but if sodium hydrogen carbonate was present, the presumably formed anion (**116**) underwent an alternative decomposition, yielding the remarkably stable nitrile oxide (**117**) [78JCS(P1)1117].

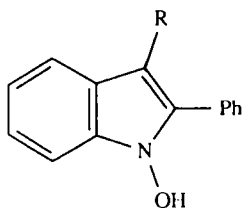
1-Hydroxy-2-phenylindole must be one of the most stable 1-hydroxyindoles yet found. It tautomerizes to the 3*H*-indole 1-oxide form; the ratio of the tautomers in solution is highly solvent-dependent and varies from 100% of **118** in DMF to 100% of **119** in methanol (81CPB1827). It was the



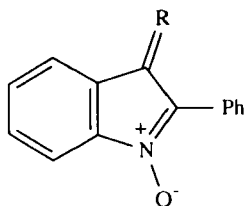
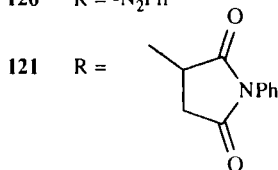
first 1-hydroxyindole synthesized in concentrated sulfuric acid solution (1895CB585; 1896CB2062). It dissolves in 5% aqueous sodium hydroxide and was recovered unchanged after heating in toluene for 2 hrs (80JOC5316); at 180°C in *p*-xylene, it gives 2,2'-diphenyl-3,3'-bisindole (65JOC3604). Oxidation by air gives a bisindole derivative (73T2425, see also Section III,D), and with cold alkaline, potassium permanganate 2-nitrobenzoic acid is obtained (1896CB2062). 1-Hydroxy-2-phenylindole, unlike its *O*-acyl derivatives, is not reduced by hydrogen over palladized charcoal (60JCS3466), but yields 2-phenylindole with zinc and acetic acid (1896CB2062) and with triethyl phosphite (65JOC3604).

Electrophiles attack 1-hydroxy-2-phenylindole at position 3; benzene-diazonium chloride gives **120** (64G1448), *N*-phenylmaleimide forms **121** (62G1401), and phosphorus oxychloride in DMF yields 2-phenylindole-3-carbaldehyde with loss of the 1-hydroxyl group (81CPB1827). Phosphorylation of the hydroxyl group and hydride transfer from the formic acid formed or present in the solvent or from the DMF itself could account for this result. Electrophilic attack from the anion of **118** in ethanolic sodium ethoxide on amyl nitrite gave **122** (04MI1; 06MI1), but amyl nitrite in ether caused oxidation to the bis-nitrone **124** and to isatogen **123** with excess reagent (39G646). These last reactions must proceed through radicals, which are readily formed from the indole (see Section III,D). The anodic oxidation of 1-hydroxy-2-phenylindole in the presence of amines such as 4-methoxyaniline yields the corresponding 2-phenyl-3-arylimino-3*H*-indole 1-oxides, e.g. **125** [83JCR(S)256], also obtained from the hydroxyin-

dole with the appropriate nitrosobenzene in the presence of sodium ethoxide (70G770). The oxidation was also effected using *N*-chlorobenzotriazole, *N*-chloroisatin, and lead tetraacetate when **125** and other compounds were obtained, but the mechanisms of the conversions of **118** to **125** could not be elucidated [86JCS(P1)607]. The hydroxyindole **118** with tetracyanoethylene gave malondinitrile and the 1-oxide **126** through a charge-transfer complex as intermediate. The X-ray crystal structures of the 1-oxide **126** (87M369) and of the complex between the indole **118** and 4-(4-dimethylaminophenyl)azopyridine have been described (83G153).

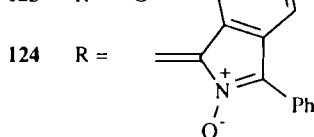


**120** R = -N<sub>2</sub>Ph



**122** R = =NOH

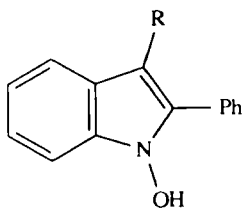
**123** R = =O



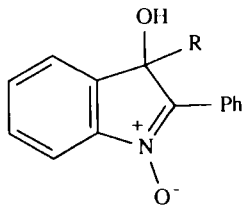
**125** R = =NC<sub>6</sub>H<sub>4</sub>-p-OMe

**126** R = =C(CN)<sub>2</sub>

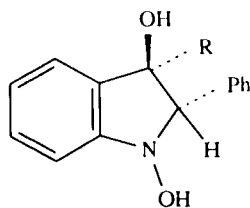
A small number of 3-hydroxy-2-phenyl-3*H*-indole 1-oxides (**128**) have been prepared [80JCS(P2)339] from the 3-substituted (R = Me or Ph) indoles (**127**) by stirring benzene solutions in air. Reduction with sodium borohydride gave the indolines **129** which, with ethanolic hydrogen chloride, gave back the indoles (**127**). The similar acid-catalyzed dehydra-



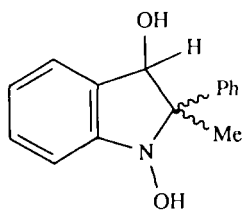
**127**



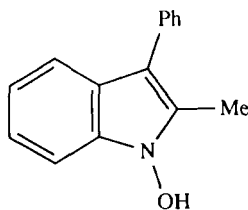
**128**



**129**



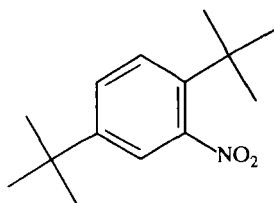
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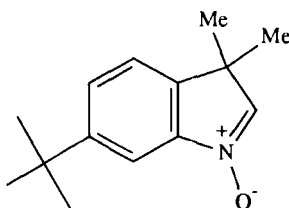
131

tion of both stereoisomers of **130** by a carbonium-mediated 1,2-shift gave **131**, which was identified from the ESR spectrum of the corresponding radical [81JCS(P1)1610].

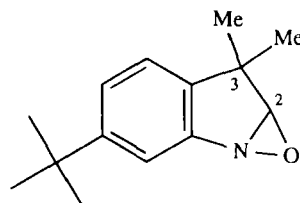
The irradiation of 2,5-*di-t*-butylnitrobenzene (**132**) gave the very unstable 3*H*-indole 1-oxide (**133**), the photoisomerization of which gave the also very unstable oxazirine (**134**). This, by a 1,2-hydrogen shift, gave the oxindole **135** (26%) and, by ring opening between positions 2 and 3 and recyclization, gave the 4*H*-3,1-benzoxazine **136** (36%) (76CB3849).



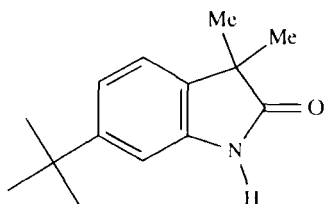
132



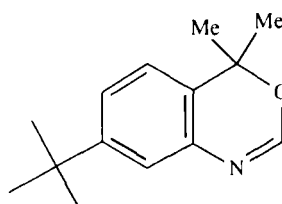
133



134



135



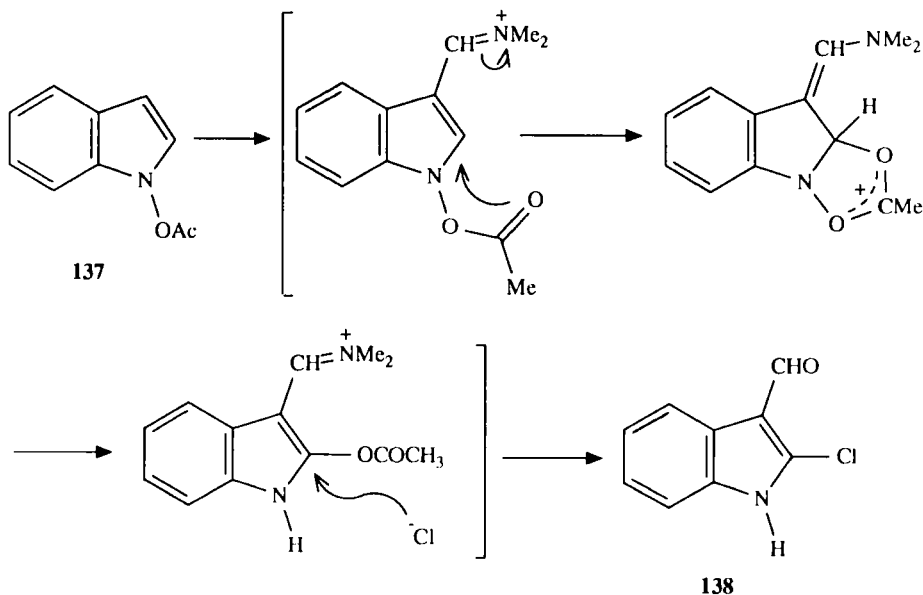
136

## 2. 1-Acyloxyindoles

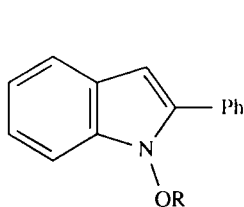
1-Acetyloxyindole (**137**) is a colorless oil that can be distilled without significant decomposition (b.p. 78–80°C at 0.1 torr) if these conditions are



not exceeded [78JCS(P1)1117; 84JCR(M)1301]. It can be kept for months, but not for years, at  $-10^{\circ}\text{C}$  under nitrogen in sealed tubes in the dark [84JCR(M)1301]. It is often used as a synthetic intermediate instead of the unstable 1-hydroxyindole, for it yields this last compound readily on alkaline hydrolysis. Many unstable 1-hydroxyindoles have therefore been converted immediately after synthesis to the acyl derivatives, which have then been isolated.



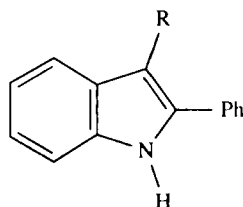
Although titanium(III) chloride is reported (81CPB726) not to reduce 1-acetyloxyindoles to the corresponding indoles, this reduction can be achieved by hydrogen over palladium on charcoal (60JCS3466). 1-Hydroxy-2-phenylindole (**139**) with benzoyl chloride and aqueous sodium carbonate or pyridine at room temperature gave the 1-benzoyloxyindole **140** in  $\sim 90\%$  yield, but if this compound is heated in DMF, an apparent 1,3-shift of the acyl group occurs to form **142** (81CPB1920). The corresponding 1-(4-nitrobenzoyloxy)indole rearranges to the 3-isomer much more easily (72T2749), but the exact mechanism of the rearrangement is not known. Treatment of **139** with tosyl chloride and pyridine also gave some **143**; the expected intermediate **141** was not detected. Carrying out the reaction with tosyl chloride in the presence of ethyl cyanoacetate (or similar compounds with activated methylene groups) gave **144**, suggesting that nucleophilic attack at position 3 with concurrent loss of the 1-substituent is a general reaction for this type of compound (81CPB1920).



139 R = H

140 R = C(=O)Ph

141 R = Tosyl



142 R = OC(=O)Ph

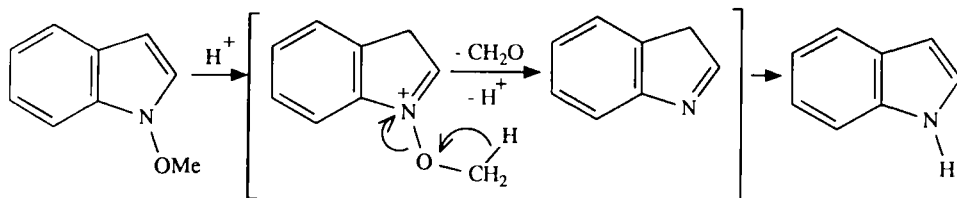
143 R = OTs

144 R = CH=CH-C(=O)OEt

1-Acetyloxyindole **137** is attacked by electrophiles at position 3; for example, chlorosulfonyl isocyanate gave 1-acetyloxy-3-cyanoindole [84JCR(M)1301], and oxalyl chloride formed 1-hydroxyindole-3-glyoxylic acid (after hydrolysis) [78JCS(P)1117], but rearrangement can also occur. With DMF and phosphorus oxychloride, below 10°C, followed by hydrolysis, a mixture of the expected 1-hydroxyindole-3-carbaldehyde (16%) and the 2-chloroaldehyde **138** (57%) was obtained, the last compound being formed by nucleophilic attack at the 2-position as shown.

### 3. 1-Methoxyindoles

1-Methoxyindole (**145**) is a colorless liquid (b.p. 47–48°C at 0.035 torr) [78JCS(P)1117], which decomposes slowly ( $t_{1/2} = 6$  hr) to indole at 150°C, but was unchanged after 8 years in storage in the absence of light [84JCR(M)1301]. In general, it has the properties of a weakly deactivated 1-substituted indole. Photolysis of 1-methoxyindole gave a tar, but that of the 2-phenyl derivative gave 3-methoxy-2-phenylindole and other compounds (73TL2451).



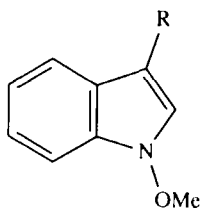
145

The 1-methoxyl group is rapidly removed by hydrogen over palladium on charcoal at room temperature and pressure to give indole. This proce-

ture has been used to demethoxylate many 1-methoxyindoles to the corresponding indoles; hydrogen over Raney nickel has also been used (62ACS1378).

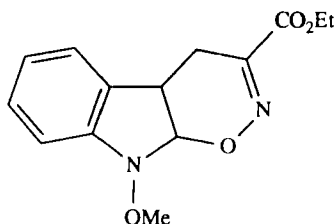
Sodium borohydride in boiling isopropanol does not affect 1-methoxyindole, and although lithium aluminum hydride in refluxing ether caused a slow reduction to indole, this reagent usually reduces other functional groups first [78JCS(P1)1117]. 1-Methoxyindole is stable to refluxing aqueous-methanolic sodium hydroxide [84JCR(M)1301], but some 1-methoxyindoles in water at 100°C under nitrogen lose formaldehyde to give the corresponding indoles, and refluxing with 1% aqueous hydrochloric acid gave the same result (65LA212). The loss of formaldehyde could occur following protonation or electrophilic attack at position 3 as indicated.

1-Methoxyindole is attacked by electrophiles at position 3 [78-JCS(P1)1117], but less easily than indole itself. It did not react with benzene diazonium chloride, or  $\beta$ -propiolactone under conditions where indole is attacked, nor with methyl iodide at 100°C in the presence of base; without base a tar lacking the methoxyl group was produced. Trifluoroacetic acid caused protonation and decomposition, while pyridinium perbromide gave an unstable 3-bromo derivative. Iodination with iodine in morpholine gave 3-iodo-1-methoxyindole (85CPB5147). The Mannich reaction gave high yields of the gramine **146**, which was converted to the methiodide **147** with excess methyl iodide under conditions where indole itself gives bis-(3-indolyl)methyl derivatives (52JA3916). This methiodide (**147**) undergoes nucleophilic displacement far less easily than the corresponding compound from indole, and although it gave **148** with diethyl sodioacetamidomalonate, all attempts to displace the quaternary nitrogen



	R		R
<b>146</b>	CH <sub>2</sub> NMe <sub>2</sub>	<b>153</b>	C(CN)=C(CN) <sub>2</sub>
<b>147</b>	CH <sub>2</sub> <sup>+</sup> NMe <sub>3</sub> I <sup>-</sup>	<b>154</b>	CHO
<b>148</b>	CH <sub>2</sub> C(NHAc)(CO <sub>2</sub> Et) <sub>2</sub>	<b>155</b>	COCO <sub>2</sub> H
<b>149</b>	CH <sub>2</sub> CN	<b>156</b>	COCH <sub>2</sub> Cl
<b>151</b>	CH <sub>2</sub> C(=NOH)CO <sub>2</sub> Et	<b>157</b>	CH=CHNO <sub>2</sub>
<b>152</b>	(CH <sub>2</sub> ) <sub>2</sub> COMe	<b>158</b>	CH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub>
		<b>159</b>	CO <sub>2</sub> H

by cyanide in the hope of obtaining **149** were unsuccessful; the methoxyl group was lost. Nevertheless 1-methoxyindole did combine with ethyl 3-bromo-2-hydroxyiminopropionate to give **150**, which in chloroform

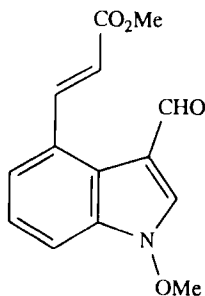


**150**

isomerized to **151**. Alkaline hydrolysis to the corresponding acid followed by concurrent decarboxylation and dehydration by acetic anhydride now gave **149** [84JCR(M)1301].

But-2-en-3-one and tetracyanoethylene attacked 1-methoxyindole to give **152** and **153**. The Vilsmeier reaction gave **154**, oxalyl chloride **155** [78JCS(P1)1117], and 1-dimethylamino-2-nitroethylene **157**, respectively (85H1101). This last compound has also been converted by sodium borohydride reduction to the nitroethane **158**, and subsequent reaction with hexamethylphosphorus triamide gave 1-methoxytryptamine (85H1101). The aldehyde **154** and the acid **155** have "normal" properties and have been much used as synthetic intermediates. The aldehyde has been reduced to the corresponding alcohol by sodium borohydride (87M13).

Thallation of 1-methoxyindole-3-carbaldehyde with thallium trifluoroacetate followed by treatment with potassium iodide gave the 4-iodo derivative in 91% yield, and this has been converted into many other 1-methoxyindole derivatives (86CPB677). When the thallated indole reacted with methyl acrylate in the presence of a catalytic quantity of palladium(II) acetate, 47% of the product was the 4-derivative **160**, but 11% of the 5-isomer was also formed (86CPB4116).

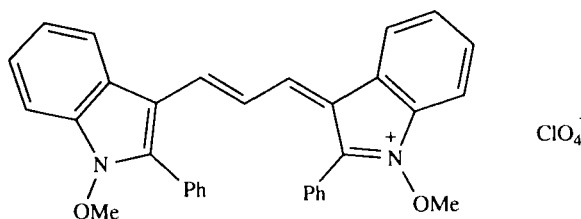


**160**

1-Methoxyindole-2-carboxylic acid is obtainable by methylation of 1-hydroxyindole-2-carboxylic acid (**100**) under basic conditions or by the hydrolysis of the ester obtained from **100** with diazomethane. It is a stable compound that is reduced to the corresponding alcohol by lithium aluminum hydride (65MI1) and converted to the acid chloride by phosphorus chlorides (1896CB646). Attempted decarboxylation gave only indole and its 2-carboxylic acid, the methoxyl group being lost (65MI1, 65MI2). Oxidation of the acid with chromic-acetic acid gave 1-methoxyisatin (1896CB646), while bromination gave the 3-bromo compound; the methyl ester, on bromination, gave the 3,5-dibromo derivative [68JCS(C)504].

1-Methoxyindole-3-carboxylic acid cannot be readily obtained by the direct oxidation of the aldehyde **154**, but oximation and dehydration to the nitrile, which has also been obtained by other routes, and alkaline hydrolysis gave the acid **159**, which has been little investigated [84JCR(M)1301].

1-Methoxy-2-phenylindole with trimethoxypropene in hot acetic acid and 48% hydrogen bromide is reported to give the highly conjugated **161**. 1-Methoxy-2-phenylindole-3-carbaldehyde gives similar compounds with heterocycles possessing activated methyl groups (71GEP1950726, 71GEP1950746).



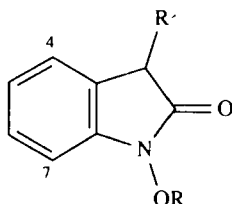
161

### C. 1-HYDROXY-2-OXINDOLES AND RELATED COMPOUNDS

1-Hydroxy-2-oxindole (**162**) gives a blue ferric chloride color, like other hydroxamic acids (63JCS4610), and is readily methylated by diazomethane, or alkyl halides and bases, and acylated to give the stable O-derivatives **163** or **164**. It is, however, converted by tosyl chloride in triethylamine to a very labile 1-tosyloxy compound (**165**), which rearranges to a mixture of 4- and 6-tosyloxy-2-oxindoles (71CC1437).

The 3-methylene group of 1-methoxy-2-oxindole (**163**) is easily ionized to give a carbanion that undergoes well-known types of reactions with alkyl halides or activated olefins without loss of the methoxyl group (e.g.

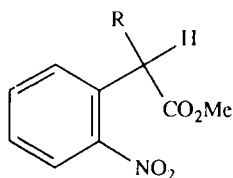
85H1101). If a 3-ester group is present in a 1-hydroxy-2-oxindole, e.g. **166**, methylation in the presence of sodium ethoxide takes place preferentially at the 3-position [67CR(C)1075]. 1-Hydroxy-4-nitro-2-oxindole with excess methyl iodide and sodium methoxide gave 57% of the expected 1-methoxy-3,3-dimethyl derivative, but surprisingly, it also gave 20% of 3-hydroxy-1-methoxy-3-methyl-4-nitro-2-oxindole (81CPB726), oxidation of a 3-carbanion having taken place. Treatment of 1-hydroxy-6-*t*-butyl-2-oxindole with thionyl chloride, presumably via a cyclic ester and ipso attack, gave 6-*t*-butyl-7-chloro-2-oxindole (78CB3806).



	R	R'
<b>162</b>	H	H
<b>163</b>	Me	H
<b>164</b>	Ac	H
<b>165</b>	Ts	H
<b>166</b>	H	CO <sub>2</sub> Et
<b>167</b>	H	NH <sub>2</sub>
<b>168</b>	H	CMeC≡H

1-Hydroxy-2-oxindoles have been obtained by five methods:

- (1) *Reduction of 2-nitrophenylacetic acids*. The best method of preparing 1-hydroxy-2-oxindole is the reduction of methyl 2-nitrophenylacetate (**169**) with zinc and ammonium chloride and immediate acetylation

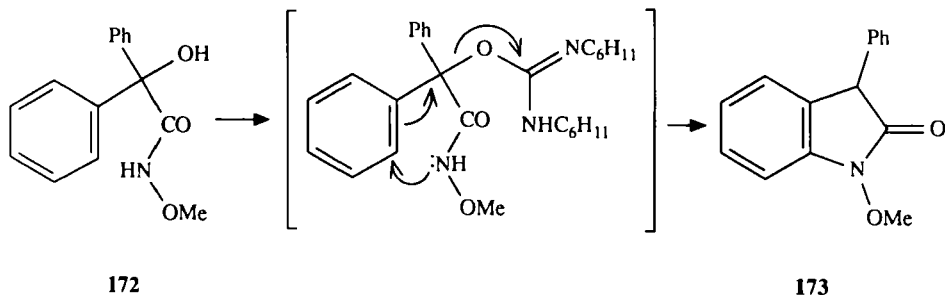


<b>169</b>	R = H
<b>170</b>	R = CMe <sub>2</sub> C≡CH
<b>171</b>	R = CO <sub>2</sub> Et

with acetic anhydride and pyridine to give 1-acetyloxy-2-oxindole (**164**). Hydrolysis with sodium carbonate now gave the hydroxy compound **162**; this method also worked well with **170**, giving **168** (85H1101). The crude mixture formed by reduction of **169** with diazomethane gave a high yield of 1-methoxy-2-oxindole (**163**) (83H1797). Sodium borohydride with palladium on charcoal reduced ester **169** to 1-hydroxy-2-oxindole in 40% yield (63JCS4610).

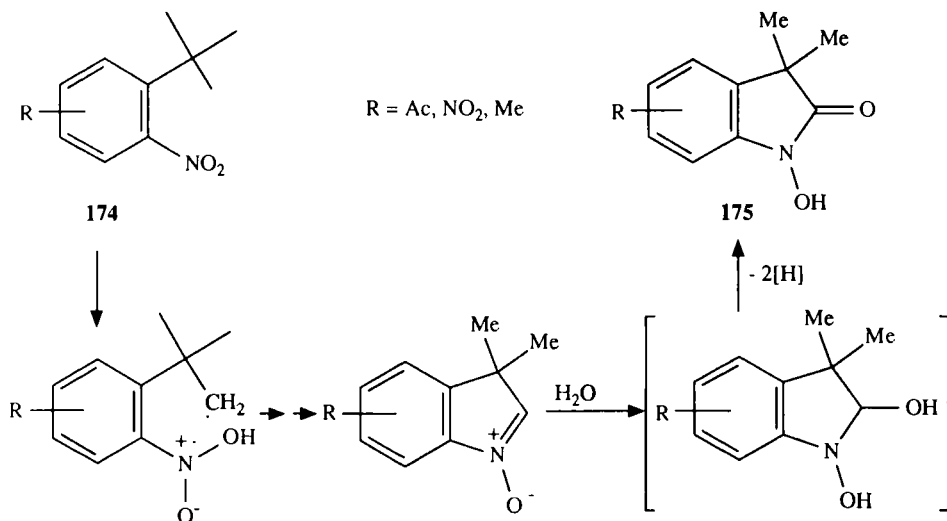
Reduction of the diethyl ester (cf. **171**) with potassium borohydride and palladized charcoal gave a high yield of the 1-hydroxy compound **166**. With hydrogen and the same catalyst, reduction to the indole occurred [67CR(C)1075], but other attempts to use this method for the partial reduction of nitro compounds to 1-hydroxy-2-oxindoles have not been very successful (e.g. 86JOC1704). The hydrogen over platinum and charcoal reduction of 2-nitrophenylglycine hydrochloride, in contrast to the palladium on charcoal reduction of 2-nitrophenylglycine which gave 3-amino-2-oxindole, gave 3-amino-1-hydroxy-2-oxindole (**167**) in 62% yield (73JMC1043); this catalyst warrants further investigation. Electrochemical reduction of 2-nitrophenylacetic acid to **162** and similar reductions have been described, but no yields were quoted [71CR(C)1378].

- (2) *Cyclization of N-alkoxyglycollic acid amides*. These amides, e.g. **172** are readily obtainable from *O*-methylhydroxylamine and the appropriate acid with dicyclohexylcarbodiimide, and on refluxing in carbon tetrachloride with the same reagent, cyclization occurs to **173** [85ZN(B)398]. A similar cyclization is effected by thionyl chloride in the presence of 1,1'-thionyl-diimidazole (86AP1084).

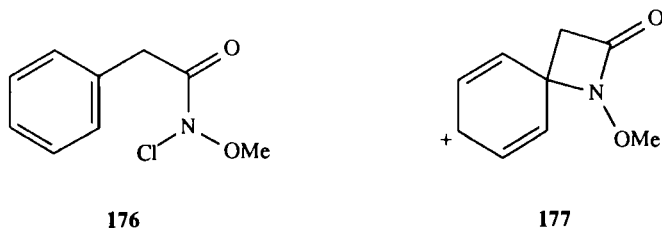


- (3) *Photolysis*. 1-Hydroxy-2-oxindole (**162**) is reportedly formed from 2-(2-nitrophenyl)ethanol by UV irradiation in several solvents (70ACS2650). The main product of the irradiation of dissolved or powdered **174** is the 1-hydroxyindolone **175**, which is formed by the initial attack of the excited nitro group on the *t*-butyl group (75CB3843). A great deal of mechanistic work has been done on

this reaction by Döpp and his collaborators; many substituted derivatives have been investigated, and it has been shown that the reaction proceeds as outlined [79LA554; 87JCS(P2)1153, and papers cited]. 2-Ethylnitrobenzene does not undergo this type of reaction (70ACS2650).

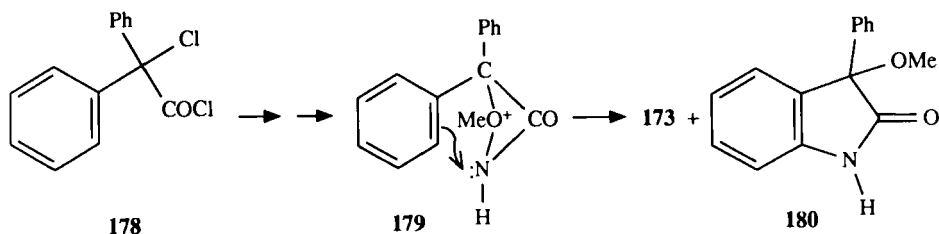


- (4) The *N*-chloro compound **176**, obtained from the corresponding methoxyamide with *t*-butyl hypochlorite, was cyclized to 1-methoxy-2-indolone **163** by silver carbonate in trifluoroacetic acid (87% yield) (84JA5728), or by other silver or mercury salts (87T2577), and more conveniently by anhydrous zinc acetate in 1,2-dichloroethane (91% yield) (87CL1771). The reaction proceeds through the spiro intermediate **177**, followed by both possible 1,2-shifts.
- (5) Treating the acid chloride **178** at  $-20^{\circ}\text{C}$  with *O*-methylhydroxylamine in ether gave a 1 : 4 mixture of the 1- (**173**) and 3-methoxy-2-oxindoles (**180**). These compounds were not interconverted on heating and so must be formed from a common intermediate, possibly **179** (72JOC2207).

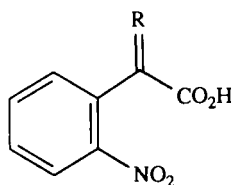
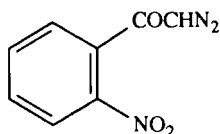
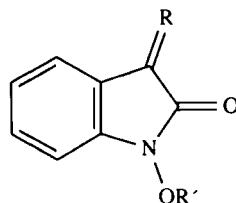




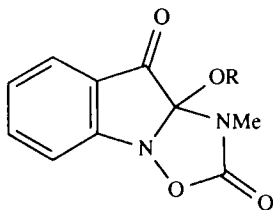
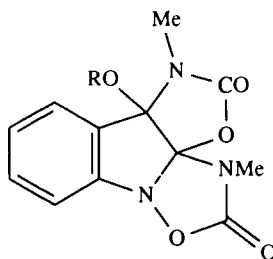
In a comprehensive review of isatins (75AHC1), only a few 1-hydroxyisatins are mentioned. The parent compound, **184**, and **185** have been obtained [71CR(C)1378] in high yield from the electrochemical reduction of 2-nitrophenylglyoxylic (**181**) and 2-nitrophenylmandelic acid (**182**), respectively, but the isatin is more commonly prepared from 2-nitrobenzoyl chloride and diazomethane. Heating the resultant diazoketone (**183**) in glacial acetic or sulfuric acid gives 1-hydroxyisatin (**184**), and on employing  $^{14}\text{CH}_2\text{N}_2$ , the label appears at the 2-position of the isatin (64T2059). The exact mechanism of the transformation is still an open question.



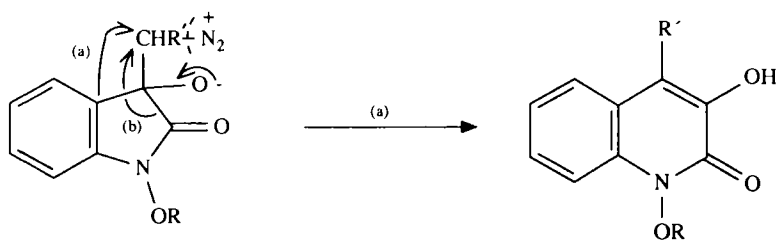
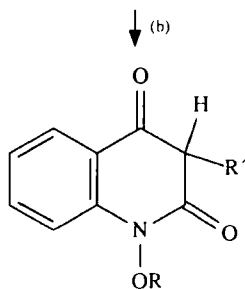
1-Hydroxyisatin (**184**) has the properties of an activated ketone (position 3) and a hydroxamic acid. Direct reduction to isatin has not been effected (64T2059), but with acetic anhydride it yields 1-acetyloxyisatin (**186**) (69-LA37), and the first product obtained with 1 mol of methyl isocyanate is the orange compound **187** (67CB3520), the formation of which is catalyzed by phenyldiazomethane. With 2 mol of methyl isocyanate, the colorless compound **189** was obtained which, in chloroform, from the IR spectrum changes observed, was thought to isomerize to **191**. Compound **187** with a trace of phenyldiazomethane isomerized to the colorless compound **188**

**181** R = O**182** H, OH**183****184** R = O, R' = H**185** R = H, OH, R' = H**186** R = O, R' = Ac**187** R = O, R' = CONHMe

which, with diazomethane, gave **190** and with methyl isocyanate gave **189**. This last compound (**189**) with diazomethane cyclized and methylated to give **192**. These transformations were all established from a consideration of the IR spectra of the compounds (67CB3520).

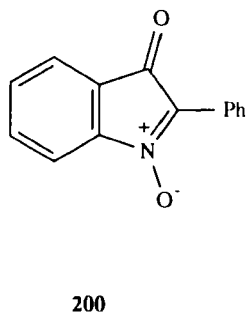
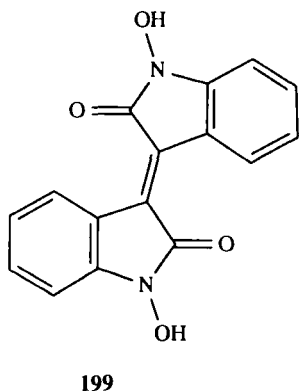
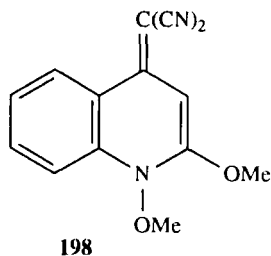
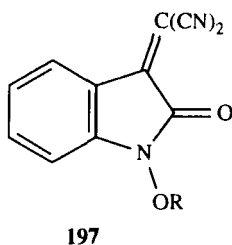
**188** R = H**189** R = CONHMe**190** R = Me**191** R = H**192** R = Me

Treatment of 1-acetyloxyisatin **186** with methanol-free diazomethane gave the diazo compound (cf. **193**) (71CB78) which, on treatment with base, gave 1-hydroxycarbostyryl **194**, also obtainable directly from 1-

**193** R = Ac, R' = H**194** R = R' = H**195** R = H, R' = PPh<sub>3</sub>**196** R = H, R' = P(OMe)<sub>3</sub>

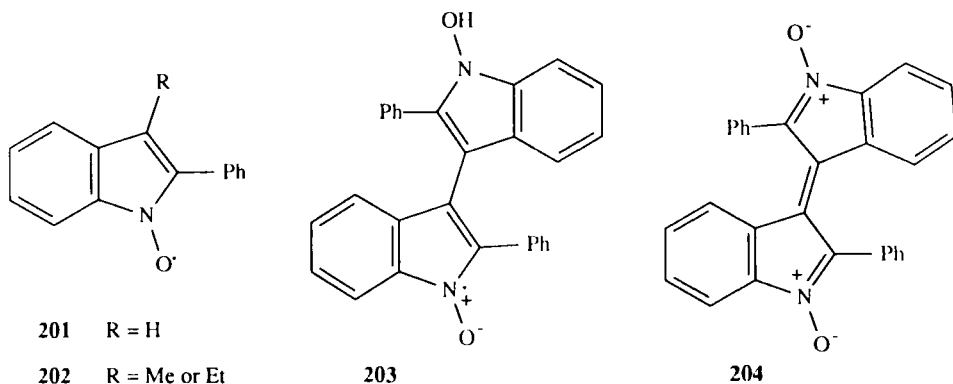
hydroxyisatin and methanolic diazomethane (69LA37). A careful study of this reaction using substituted diazomethanes (69LA37) has shown that the first formed intermediate, e.g. **193**, usually rearranged by route (a) to give the carbostyrils **194**, which are sometimes further O-methylated, but rearrangement by route (b) is followed to an increasing extent as the substituted diazomethane becomes more sterically congested. Route (a) is, however, followed when 1-hydroxyisatin **184** (or **186**) is treated with diazomethylphosphine oxide or dimethyldiazomethylphosphonate to give **195** and **196**, respectively (76LA225).

3-Dicyanomethylene-1-hydroxy-2-oxindoles (**197**), formed from 1-hydroxyisatin (or derivatives) with malondinitrile, react with diazomethane exclusively by pathway (b) to give, in this case, **198** (72CB3407). Basic hydrolysis of 3-dicyanomethylene-1-hydroxy-2-oxindole derivatives can lead to quinoline 1-oxides (76CB723). 1-Hydroxyisatin-3-hydrazones with diazoalkanes give a variety of products (71CB2221). 1-Hydroxyisatin reacts with 1-hydroxy-2-oxindole under acid catalysis to give 1,1'-dihydroxyisaindigo (**199**), and other similar condensations have been effected (69CB3691). Isatogens (e.g. **200**) have been reviewed (78AHC123) and will not be considered here.



## D. RADICALS

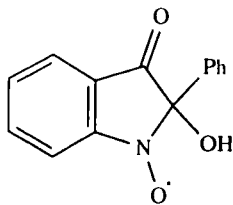
The instability of 1-hydroxyindole itself may well be due, in part, to radical formation and polymerization. Attempts to prepare a recognizable radical from this substance or its 1-*O*-acetyl derivative in an ESR spectrometer were unsuccessful (82TH1). The oxidation of the sterically hindered 1-hydroxy-2-phenylindole by a variety of reagents (83G481, and earlier papers cited) leads to the nitrone **204**, but with air and lead dioxide, it appears that the radical **201** forms first, converts to **203**, and then gives the nitrone **204** (73T2425); this nitrone always contains ~0.1% of the



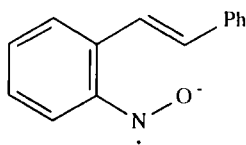
radical **203** [68JCS(B)1311]. In the absence of air, the lead dioxide oxidation is stated [67JCS(B)1072] to give the isatogen radical **205**, but this substance may be an open-chain nitroxide (**206**), while **205** is actually thought (73T2425) to be a thermolysis product of **201** in aromatic solvents. Treatment of 1-hydroxy-2-phenylindole with potassium *t*-butoxide in DMSO gave **206** (73T2425). Although radical **201** has not been detected, the corresponding 3-substituted radicals **202** have been obtained [80JCS(P2)339] by oxidation of the appropriate 1-hydroxyindoles with lead dioxide, and their ESR spectra and those of some related compounds have been recorded [81JCS(P1)1610].

Oxidation of a series of 1-hydroxy-2-indolinones by lead tetraacetate or dioxide gave the corresponding radicals exemplified by **207** (77G154) and **208**, which were identified from their ESR spectra (74T739), while chloranil oxidized 1,3-dihydroxy-2,3-diphenylindoline to **209** [80JCS(P2)339].

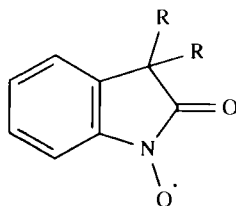
Isatin, and a number of derivatives, have been oxidized by lead dioxide to the radicals **210** and **211**, which were not very stable but their ESR spectra were measured and analyzed (77G154). While isatin itself reacts with nucleophilic amines at position 3 (cf. **211**), the corresponding radical



205



206

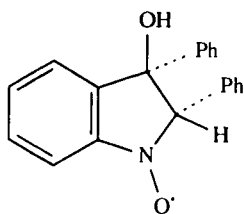


207 R = H

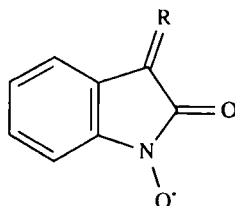
208 R = Me

**210** combined with aliphatic amines in benzene solutions to give the isomeric radicals **212**, as shown by analysis of their ESR spectra (76T159).

The reduction of 2-phenylisatogen by potassium *t*-butoxide in DMSO or polarography gave the radical **213**, and related compounds gave similar radicals (73T2425).

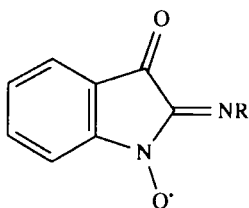


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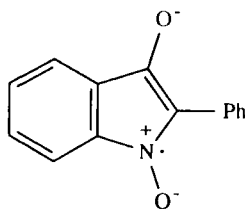


210 R = O

211 R = NR



212



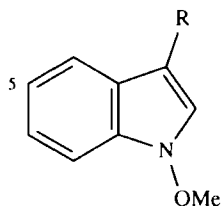
213

## E. NATURALLY OCCURRING 1-HYDROXYINDOLE DERIVATIVES

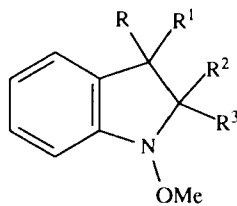
### 1. Simple Indoles

Only one 1-hydroxyindole, a complex antibiotic that will be considered later, has been obtained from natural sources, while a number of 1-

methoxyindoles have been isolated and identified. 1-Methoxyindole-3-acetonitrile (**214**), along with indole-3-acetonitrile, was obtained from the roots of *Brassica pekinensis* infected by *Plasmodium Brassica Woronin* and identified from its spectra (70ABC1590), which were essentially the same as those of synthetic material [84JCR(M)1301] (see also Section III,B). 1,5-Dimethoxygramine (**215**, 5-MeO), which has been synthesized from 1,5-dimethoxyindole, formaldehyde, and dimethylamine [78JCS(P1)1117], was first isolated from *Gymnacrancheria paniculata* and identified from its spectra and its very rapid and quantitative hydrogenation over palladium on charcoal to 5-methoxygramine (67AJC1737). *N,N*-Dimethyl-1-methoxytryptamine (lespedamine) **216** was isolated from *Lespedeza bicolor. var. japonica* and identified from its rapid conversion to *N,N*-dimethyltryptamine by hydrogenation over palladium on charcoal, or much more slowly by lithium aluminum hydride, or by heating to 100°C in water under nitrogen when formaldehyde was eliminated and identified (66LA194). The loss of formaldehyde may proceed via 3-protonation (see Section III,B).



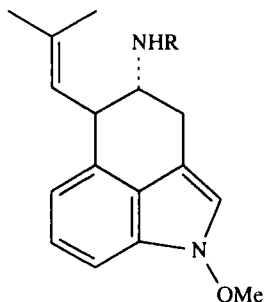
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**214** CH<sub>2</sub>CN**215** CH<sub>2</sub>NMe<sub>2</sub>**216** (CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>**217** CHO**218** CH=CHNO<sub>2</sub>**219** (CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>**220** (CH<sub>2</sub>)<sub>2</sub>COMe**221** (CH<sub>2</sub>)<sub>2</sub>CHMeCN**222** (CH<sub>2</sub>)<sub>2</sub>CHMeCH<sub>2</sub>OH**223** R = R<sup>1</sup> = H, R<sup>2</sup>, R<sup>3</sup> = O**224** R, R<sup>1</sup> = -(CH<sub>2</sub>)<sub>2</sub>-  
R<sup>2</sup>, R<sup>3</sup> = O**225** R = R<sup>2</sup> = H,  
R<sup>1</sup> = (CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>, R<sup>3</sup> = OH

Lespedamine (**216**) was first synthesized [78JCS(P1)1117] from 1-methoxyindole-3-carbaldehyde **217**, which was itself isolated from *Brassica oleracea* (cauliflower) (87MI4) by treatment with nitromethane, giving the expected nitroethylene (**218**), lithium aluminum hydride reduc-

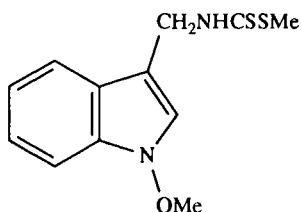
tion to **219**, and successive reaction with methyl chloroformate and lithium aluminum hydride (twice). Later, a more efficient synthesis was developed (83H1797) from 1-methoxy-2-oxindole (**223**) which, with sodium hydride and ethylenedibromide, gave **224**. Opening of the cyclopropane ring with dimethylamine followed by lithium aluminum hydride reduction gave the indoline **225**, dehydrated by brief hydrochloric acid treatment to **216**. Paniculidine B (**222**) has been isolated (85CPB1770) was an optically active oil from *Murraya paniculata* Linn. Jack and identified from its spectra and hydrogenation over palladium on charcoal to the des-methoxy compound, the structure of which had been established. Racemic paniculidine B has now been synthesized (85CPB5147) from the ketone **220**, obtainable from 1-methoxyindole by iodination and treatment with 3-buten-2-ol and tetramethylammonium bromide (85CPB5147) or by reaction with methyl vinyl ketone [78JCS(P1)1117]. The ketone was converted by tosylmethyl isocyanide to the nitrile **221** which, on successive reduction with "dibal" and sodium borohydride, gave racemic **222**.

Synthesis of the 1-methoxy analogue of ( $\pm$ )-6,7-secoagroclavine **226** and its des-methyl derivative (**227**) have been developed from 2-nitrotoluene, proceeding through 1-methoxyindole in nine steps with an overall yield of 20% (86CPB677).



**226** R = Me

**227** R = H



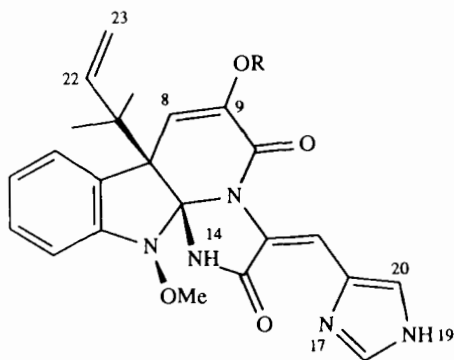
**228**

A dithiocarbamate, named 1-methoxybrassinin (**228**), along with its 1H-parent, has been isolated from *Brassica campestris* (Chinese cabbage) infected with *Pseudomonas cichorii*. These compounds are not derived from glucosinolates (see Section IIIE,5) and possess moderate antifungal activity (86CC1077).

## 2. 1-Methoxyindoline Derivatives

Three closely related 1-methoxyindolines have been isolated from *Penicillium* species. The structure of oxaline **229** from *P. oxalicum* was first

determined from an X-ray crystal structure analysis (74CC1021). Subsequently, detailed  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR analyses and other spectral and chemical studies were described (76T2625). Oxaline is not affected by 3-chloroperbenzoic acid nor in ethanol by hydrogen over platonic oxide, but in acetic acid solution the 22,23-double bond was reduced. The dihydro compound was brominated at position 20 of the imidazole ring by pyridinium bromide perbromide. Oxaline was stable (99%) to powdered alkali at  $180^\circ\text{C}$  for 3 min and completely stable to attempted drastic reduction with lithium aluminum hydride in dioxane or tetrahydrofuran. With diazomethane the 14-nitrogen was methylated, and with acetic anhydride the 19-nitrogen was acetylated. Oxaline was extremely labile towards dilute mineral acids, and with 20% hydrochloric acid the orange azacarbazole (**233**) was formed (80CPB2987).

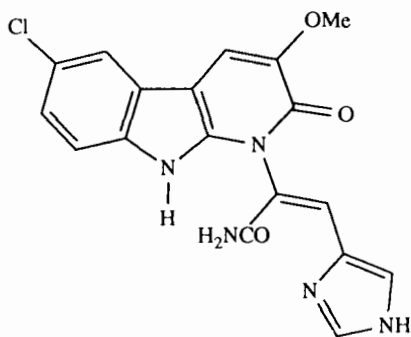


**229** R = Me

**230** R = H

**231** R = H, 8, 9 -  $\text{H}_2$

**232** R = Ac



**233**

Neooxaline has been obtained (80CPB2987) from *Aspergillus japonicus* and identified as **231** (undefined stereochemistry). With acetic anhydride in DMSO, it gave mainly **232** which, on alkaline hydrolysis, gave **230**. Compound **230**, like oxaline, with diazomethane gave 14-methyloxaline.

Later *P. meleagrinum* Biørge yielded meleagrins, a des-methyl oxaline (**230**) (84CPB94), the structure of which was established by the X-ray crystallographic analysis of the 9-*O*-(4-bromobenzoyl) derivative formed with 4-bromobenzoyl chloride in pyridine. Diazomethane, under the conditions used, methylated the 14-N atom, leaving the 9-hydroxyl group alone, thereby frustrating the attempt to convert meleagrins into oxaline.

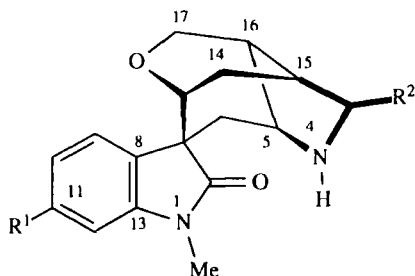


These alkaloids possess most unusual structural features, namely the 1-methoxyindoline ring, the two nitrogen atoms directly attached to position 2 of this ring, giving a triaminomethane type of structure, and a dimethylallyl group at position 3 of the indole system. A related alkaloid, roquefortine, has been isolated (76E140) from *Penicillium roqueforti*, but does not possess a 1-methoxyl group.

### 3. 1-Methoxy-2-oxindoles

About a dozen 1-methoxy-2-oxindole alkaloids have been isolated and identified, either by X-ray crystallography or by sophisticated spectroscopy. Most are associated with their des-1-methoxy analogues in the plants. Very little chemistry involving the 1-methoxy-2-oxindole ring system of these compounds has been done, and they will therefore be considered only briefly.

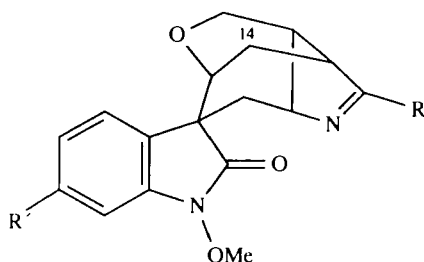
Gelsemicine (**234**) was the first naturally occurring 1-methoxy-2-oxindole to be discovered in *Gelsemium sempervirens* roots (65MI3). Its structure



- 234  $R^1 = \text{OMe}, R^2 = \text{Et}$   
 235  $R^1 = \text{OMe}, R^2 = \text{Et}, 14\beta\text{-OH}$   
 236  $R^1 = \text{H}, R^2 = \text{Et}$   
 237  $R^1 = \text{H}, R^2 = \text{Et}, 14\text{-OH}$

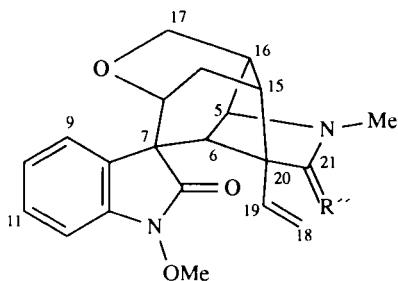
was deduced from an X-ray crystal structure study of its *N*-methyl hydride (62AX301). The 14-hydroxy derivative (**235**) has also been isolated and identified mainly by mass spectrometry (73M99). The related gelsidine (**236**) was identified by a series of spectral comparisons and by the removal of the 1-methoxyl group with lithium in liquid ammonia (62JOC4123). ( $\pm$ )-20-*epi*-Gelsedine has been synthesized [87DIS(B)139]. 14- $\beta$ -Hydroxygelsedine (**237**), also from *G. sempervirens*, was identified mainly from its  $^1\text{H}$ -NMR and 2-D COSY spectra (85MI1). Gelsenicine **238** has been obtained (82MI5) from *G. elegans* and identified by conversion to

gelsidine **236**, and the related dehydrogelsemicine (**239**) has been found in the roots of *M. brunois* [80CR(C)191].



**238** R = Et, R' = H

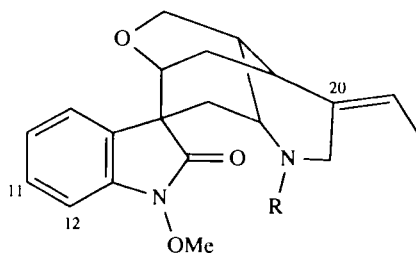
**239** R = Et, R' = OMe



**240** R'' = H<sub>2</sub>

**241** R'' = O

Gelsevirine **240** has two  $sp^3$ -carbon atoms not bearing hydrogen atoms, was isolated from *G. sempervirens*, and was identified mainly from mass and NMR spectrum comparisons (72E377; 73M87). The 21-oxo derivative **241** was obtained from the American *G. rankinii* (86MI1) and the 19-hydroxy-18,19-dihydro derivative from *G. elegans* (87CPB4668). *G. elegans*, from China, has also given humantenine **242**, the structure of which came from X-ray crystallography (84MI3; 87MI1), and humantenirine **243** (86JNP806). *G. rankinii* has now yielded rankinidine **244** (86MI2). Humantendine appears to be the 14-hydroxy derivative of **238** (84MI2) and was obtained from *G. elegans* along with humantenine (82MI3; 83MI1).



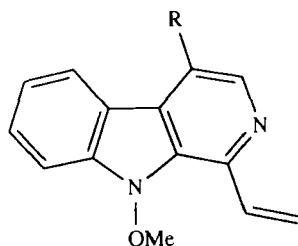
**242** R = Me

**243** R = H, 11 - OMe

**244** R = H

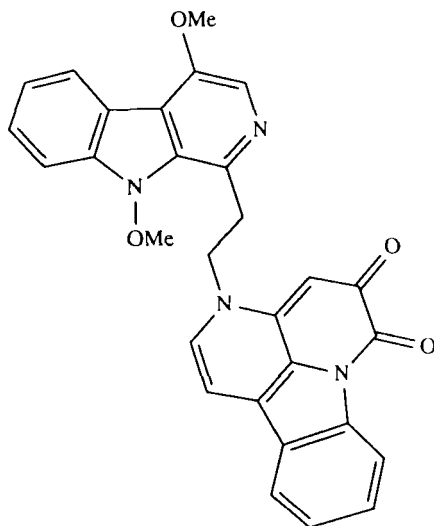
#### 4. 1-Methoxycarbolines

These compounds are pyrido[*c*,*b*]indoles and the first to be identified (**245**) was isolated from *Picrasma excelsa* (78TL2777). Subsequently, the 4-methoxy derivative **246** (83CPB3198), which was a powerful inhibitor of cAMP phosphodiesterase (84CPB1872), and picrasidine **247** (85CPB4901) were also obtained.



**245** R = H

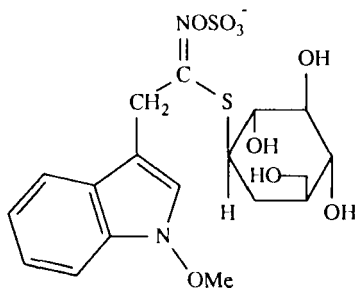
**246** R = OMe



**247**

#### 5. Glucosinolates

Indole glucosinolates have attracted attention, as they appear to be precursors of anticancer factors (81MI1; 83MI2), and their potential toxic-



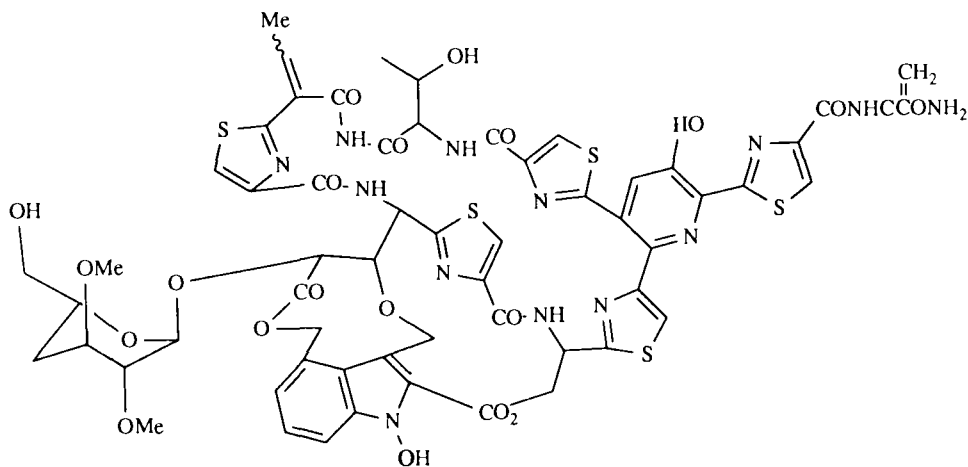
**248**

ity in "mustard oil glucosinolates" present in *Brassica spp.* vegetables such as cauliflower, salad vegetables, relishes, horseradishes, rape seed oil, etc., has led to the development of sophisticated analytical methods for these compounds (e.g. 80M11; 82T353; 84M11, 84M14, 84M15; 87M12). It seems that their breakdown products are the main source of their biological activities (86M143). About 100 glucosinolates have been described (83M12) (cf. **248**, where the indole system can be otherwise substituted or replaced by many other groups).

Neoglucobrassicin **248** is the only 1-methoxyindole derivative of this class of compounds clearly identified so far, and along with glucobrassicin, which possesses a hydrogen atom instead of the methoxy group, has been detected in many *Brassica* species. It was originally isolated from *Brassica rapus* and identified by Gmelin and Virtanen (62ACS1378). Attempts to produce suitable crystals of the brucine salt for an X-ray structure investigation have not yet been successful (86UP1). With Raney nickel and hydrogen, **248** gave some skatole and tryptamine, while heating alone gave a material which appeared to be 1-methoxyindole-3-acetonitrile from mass spectrum comparisons.

## 6. Antibiotics

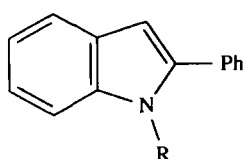
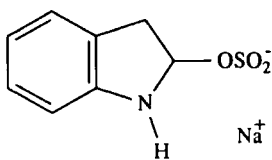
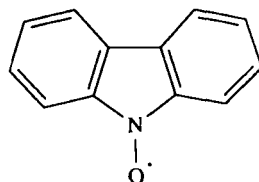
A 1-hydroxyindole-2-carboxylic acid derivative (**249**) has been isolated from a *Micromonospora globosa* culture and has very wide antibiotic activities against pathogenic gram-positive bacteria (84USP4478831).



## F. BIOSYNTHESIS AND METABOLISM

In view of the existence of a significant number of 1-methoxyindoles in plants, the possibility that these are formed by the direct *in vivo* oxidation and subsequent methylation of the corresponding 1-H compounds, which invariably accompany the 1-methoxy compounds, must be considered. The direct chemical oxidation of an indole to the corresponding 1-hydroxyindole has never been achieved, many failures have been reported, and claims of success later disproved. Nevertheless, the oxidation of 2-phenylindoline to 1-hydroxy-2-phenylindole has been effected in very poor yield (74CC677). However, 2-phenylindole (**250**) is converted to the 1-hydroxy derivative **251** by microsomal preparations of rabbit and guinea pig liver and colonic mucose homogenates (78M111). Under comparable conditions, tryptamine was hydroxylated at the primary aliphatic amino group, so it would seem that the 1-hydroxylation of the indole ring is not a favored enzymic process.

Among other biosynthetic routes to 1-hydroxyindole derivatives that may be considered is the 2,3-reduction of an indole to the corresponding indoline, N-oxidation of the (now) secondary aliphatic-aromatic amino group, possibly followed by immediate O-methylation and oxidation leading to rearomatization. The reduction-oxidation process could also be effected by an addition-elimination sequence. Addition of a proton to position 3 of the ring and an anion to position 2, as occurs in the addition of sodium hydrogen sulfite to indole giving **252** (62CB2205), followed by

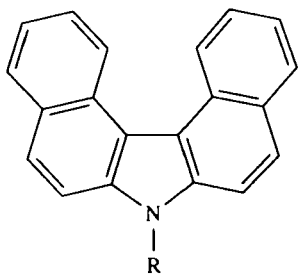
**250** R = H**251** R = OH**252****253**

N-oxidation and reversal of the addition reaction, could also lead to 1-hydroxyindole derivatives. Oxidation of an aromatic amino group to the hydroxylamine stage, or partial reduction of a nitro group to this stage instead of to the corresponding amine, prior to cyclization *in vivo* are also possibilities. In the mammalian metabolism of tryptophane, a significant amount is unaccounted for and might be metabolized through a 1-N-oxidation process. Much remains to be discovered concerning the biochemistry of 1-hydroxy- and 1-methoxyindoles, and in view of the wide

distribution of glucobrassicin in vegetables eaten by man and the possible tumor-inhibiting effect of some 1-methoxyindoles, it is an area awaiting investigation where really useful discoveries might be made.

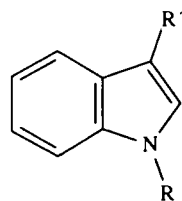
In contrast to indole itself, benzo[*b*]indole, or carbazole, is converted into carbazole 9-oxyl **253** by English sole (85M12), and the same radical is found in sole affected by carcinomas (see Section V). The enzymic oxidation by cytochrome P<sub>450</sub> of the related 7*H*-dibenzo[*c,g*]carbazole **254** in rat hepatocytes has been investigated and found to cause hydroxylation at the 2-, 3-, and probably 4- and 7-positions (83M13). The metabolism of **254** in perfused rabbit lungs and in rat liver microsomes gave the 7-hydroxy derivative **255** as a major metabolite, and a large amount was found in the rabbit tracheobronchi, which suggests it is associated with the high incidence of respiratory tract tumors caused by **254** (81M12).

1-Acetyloxyindole (256), when fed to rats, caused an increase in the urinary excretion of indole, indoxyl sulfate (**258**), and anthranilic acid, but 1-methoxyindole (**257**) was almost completely converted to **258** and anthranilic acid, no indole being detected (84M17). Feeding the rats 1-



**254** R = H

**255** R = OH



R R'

<b>256</b>	OAc	H
<b>257</b>	OMe	H
<b>258</b>	H	OSO <sub>3</sub> H
<b>259</b>	H	CO <sub>2</sub> H
<b>260</b>	OH	CO <sub>2</sub> H
<b>261</b>	OMe	CO <sub>2</sub> H
<b>262</b>	H	COCO <sub>2</sub> H
<b>263</b>	OH	COCO <sub>2</sub> H
<b>264</b>	OMe	COCO <sub>2</sub> H
<b>265</b>	OMe	CH <sub>2</sub> OH
<b>266</b>	OMe	CHO

hydroxyindole-3-carboxylic acid (**260**) gave indole-3-carboxylic acid (**259**) and its glucuronide, but no methylation to the 1-methoxy compound (**261**) could be detected. This last compound (**261**) was converted to indole-3-carboxylic acid (**259**) and to relatively large amounts of its glucuronide and the glucuronide of **261** in the rat (84MI7). Indole-3-glyoxylic acid (**262**) and its 1-methoxy derivative (**264**) were excreted unchanged, but significant reduction of the hydroxy acid **263** to **262** took place. The high stability of these compounds in the rat has been associated with their high acidities ( $\text{pK}_a \sim 2.0$ ) (84MI7). One can conclude that in mammals, reductive demethylation of ingested, naturally occurring 1-methoxyindoles to the corresponding indoles probably takes place. It has also been pointed out (84MI7) that as 1-acetoxy- and 1-methoxyindole cause no mutations in the Ames test, this nucleus is unlikely to be carcinogenic, and the synthesis of 1-methoxy-, 1-acetoxy-, or other 1-substituted-oxy-indoles as pro-drugs (75MI1) for valuable indolic medicinal agents, or in their own right, might well be worthwhile. A start in this area has subsequently been made (86CPB677).

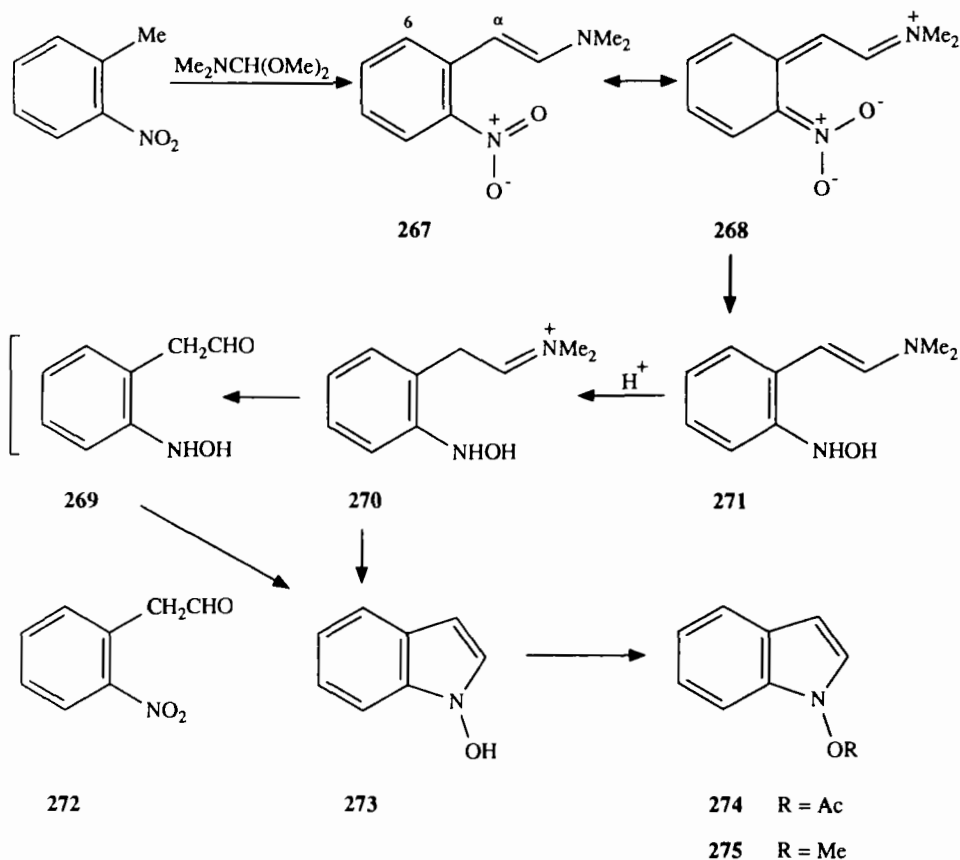
1-Methoxyindole-3-carbinol (**265**), the 3-carbaldehyde (**266**) which is present in *Brassica oleracea* (cauliflower), and some other indoles given by oral intubation to rats caused significant increases in hepatic ethoxyresorufin *O*-de-ethylase activity, which may be related to their inhibitory effect on tumorigenesis in these animals by polycyclic aromatic hydrocarbons (87MI3). It is thought that this effect may be due to unidentified acid-catalyzed condensation products of these indoles formed in the stomach. Dietary exposure to the aldehyde **266** in rats can lead to significant alterations in their cytochrome  $\text{P}_{448}$ -dependent monooxygenases (87I4).

## G. SYNTHETIC METHODS

### 1. Reduction of 2-Nitrophenylacetaldehydes

The best method [81H1523; 84JCR(M)130] for preparing 1-hydroxyindole (**273**) starts from 2-nitrotoluene, which can be converted to enamine **267** in very high yield by heating with DMF dimethylacetal and distilling off methanol as it is formed. The deep red enamine (**267**) is stabilized by resonance (**268**) [84JCR(M)1301] and cannot be hydrolyzed to 2-nitrophenylacetaldehyde (**272**) under conditions that do not polymerize this aldehyde, but reduction with zinc and ammonium chloride in an ether-water two-phase system until the enamine had disappeared gave an ether solution of 1-hydroxyindole. Presumably, reduction as indicated to the hydroxylamine **271**, in which the enamine system is not resonance-

stabilized, now leads to protonation (**270**) and direct cyclization, or hydrolysis to the aldehyde **269** and subsequent cyclization. Attempts to isolate the indole from the solution gave a green polymer [78JCS(P1)1117], but acetic anhydride and sodium hydrogen carbonate, or methyl iodide and sodium methoxide, gave the derivatives **274** and **275**, respectively, which have been prepared on a 50 g scale. A convenient one-pot method has been worked out (86CPB677).



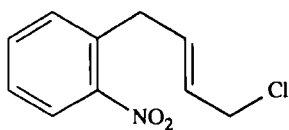
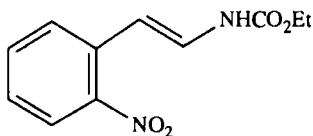
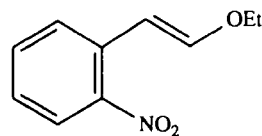
This general method has been used for making various 1-hydroxyindoles including the 4-nitro, 4- and 5-methoxycarbonyl, 4-benzyloxy, and 6-carbaldehyde derivatives (81CPB726; 86CPB4109, 86CPB4116). When the enamine (cf. **267**) bears a substituent that prevents the dialkylaminovinyl side-chain from becoming roughly coplanar with the nitro group, then resonance of the type shown becomes impossible. Protonation and hydrolysis then occur under mild or very mild conditions, yielding the corre-



sponding 2-nitrophenylacetaldehydes (cf. **272**). Examples are the 6-nitro and the  $\alpha$ -methyl derivatives of **267** [84JCR(M)1301] along with the 6-benzyloxy derivative, which is even hydrolyzed to the aldehyde by water and silica gel (81CPB726).

Titanium(III) chloride has been carefully examined (81CPB726) as a reducing agent for E-2,6-dinitro- $\beta$ -dimethylaminostyrene. With 12 mol, only 4-aminoindole (84%) was obtained, while with 4 mol, the main products were 1-hydroxy-4-nitroindole (57%), 1-hydroxy-4-nitro-2-oxindole (16%), and 4-nitroindole (13%). The formation of the oxindole was not explained, but it most likely arises from an intramolecular oxidation of the intermediate aldehyde by the nitro group. The same reagent also converted E-5-methoxycarbonyl-2-nitro- $\beta$ -dimethylaminostyrene into the corresponding indole (49%) and 1-hydroxyindole (26%) (86CPB4116). In the case of E-2-benzyloxy-6-nitro- $\beta$ -dimethylaminostyrene, reduction by titanium trichloride, or by zinc and ammonium chloride, gave identical yields of the 1-acetyloxyindole (81CPB726), while better results were obtained using the zinc method with E-6-methoxycarbonyl-2-nitro- $\beta$ -dimethylaminostyrene (81CPB726) and 4-formyl-2-nitro- $\beta$ -dimethylaminostyrene (86CPB4109). The hydrogenation of E-2-nitro- $\beta$ -dimethylaminostyrenes over palladium on charcoal led to indoles, but 1-hydroxyindoles were also isolated if the hydrogen pressure was low, if only a small amount of catalyst was used, and if the enamine possessed a strongly electronegative substituent (e.g. NO<sub>2</sub>, CN, CO<sub>2</sub>Me, at the 5- or 6-position) (85JHC121).

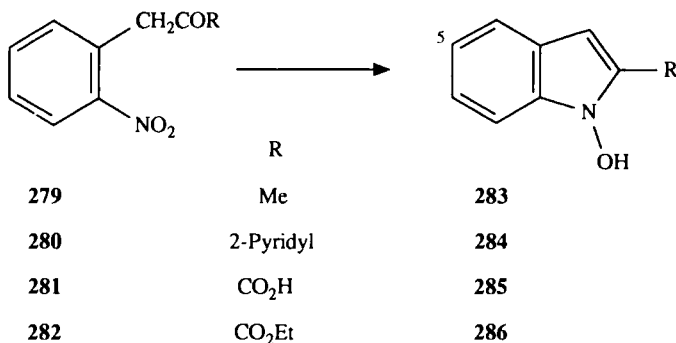
Alternative methods of preparing 2-nitrophenylacetaldehydes for the 1-hydroxyindole synthesis have been used. 2-Nitrobenzenediazonium chloride and a number of substituted derivatives have been coupled with butadiene to give chlorobutenes (e.g. **276**) which, on ozonolysis or osmium tetroxide-periodate treatment, gave the aldehydes (e.g. **272** [78JCS(P1)1117]. Hydrolysis of ethyl 2-(2-nitrophenylvinyl)carbamate (**277** to 2-nitrophenylacetaldehyde has been reported (67BSF1296), but could not be repeated [78JCS(P1)1117], and 2-nitrophenylacetaldehyde was obtained, presumably via **278**, from 2-nitrobenzenediazonium chloride and ethyl vinyl ether [78JCS(P1)1117].

**276****277****278**

## 2. Reduction of 2-Nitrophenyl Ketones

Since both 2-nitrophenyl ketones and 2-substituted-1-hydroxyindoles are far more stable than the corresponding aldehydes and 2-H indoles, respectively, reduction of these ketones to the 1-hydroxyindoles is relatively easy.

The zinc and ammonium chloride reduction method discussed previously converted methyl 2-nitrobenzyl ketone (**279**) into the 1-hydroxyindole **283** [67BSF1296; 70JCS(C)1067], while sodium borohydride with palladium on charcoal reduced **280** to **284** (65JCS1706). Sodium amalgam was used by Reissert (1897CB1030) to reduce 2-nitrophenylpyruvic acid (**281**) to the carboxylic acid **285**. Hydrogen over platinum has also been used [67JCS(C)2246] to reduce **281** or its oxime, phenylhydrazone, or semicarbazone to **285** (21JCS1607). Good results have been obtained using magnesium amalgam in the reduction of the appropriate 2-nitrophenylpyruvic acids to the 5- and 6-bromo derivatives of **285** [68JCS(C)504]; the reduction of the ethyl ester **282** and some derivatives by 8% sodium amalgam gave the corresponding acids (cf. **285**) (67BCJ2703).

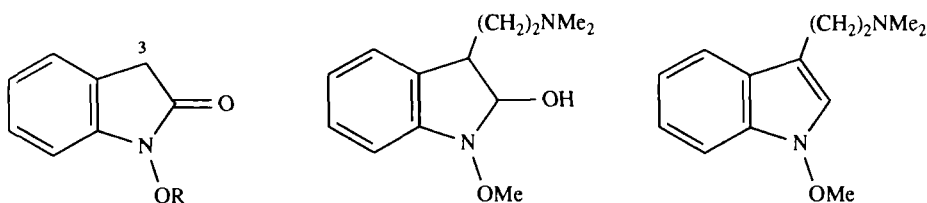


Hydrogenation of the ethyl ester (**282**) over Adams catalyst (PtO<sub>2</sub>) or palladium on charcoal gave a mixture of **286** and the corresponding 1H-indole [67JCS(C)2246; 73MI1], while reduction of **281** with ferrous sulfate and ammonia gave only indole-2-carboxylic acid (21JCS1607). Reduction of ethyl 4-(2-nitrophenyl)acetoacetate with hydrogen over palladized charcoal gave (76CB3282) mainly ethyl 2-indoleacetate, but 9% of the 1-hydroxy derivative was also obtained.

The polarographic reduction of a number of 2-nitrobenzyl ketones is stated (73BSF3040) to give quantitative yields of 1-hydroxyindoles, but it proved difficult to isolate the products; over reduction gave indoles.

### 3. Reduction of 1-Hydroxy-2-oxindoles

The lithium aluminum hydride reduction of 1-acetyloxy-2-oxindole (**287**) gave a polymer, but that of the 1-methoxy analogue (**288**) yielded [78JCS(P1)1117] 1-methoxyindole. Application of this method (83H1797) led to a valuable synthesis of lespedamine **291**. Alkylation of **288** by 1,2-dibromoethane and sodium hydride gave a 3,3-spiro derivative, which dimethylamine converted to **289**. Reduction with lithium aluminum hydride now gave **290**, as a mixture of isomers, which was dehydrated instantly by acid to **291** (see Section III,E).



**287** R = Ac

**290**

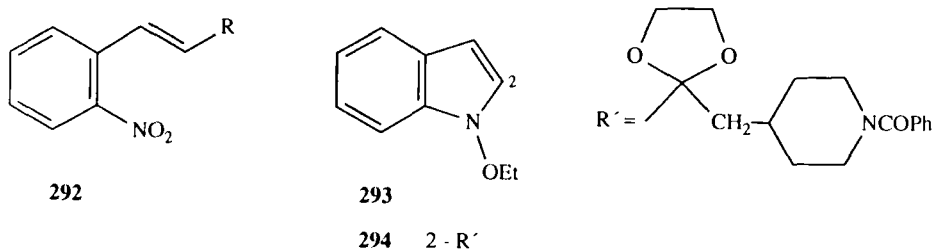
**291**

**288** R = Me

**289** R = Me, 3-(CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>

### 4. Reduction of 2-Nitrophenylethylenes

Triethyl phosphite has reduced (68JOC487) 2-nitrophenylethylenes (e.g. **292**) to mixtures containing a few percent of 1-ethoxyindoles, e.g. **293** and **294**.



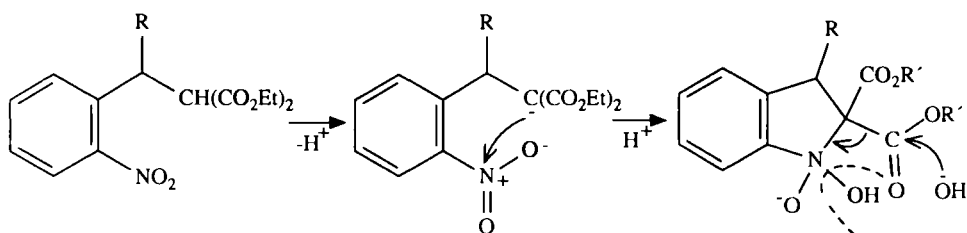
**292**

**293**

**294** 2 - R'

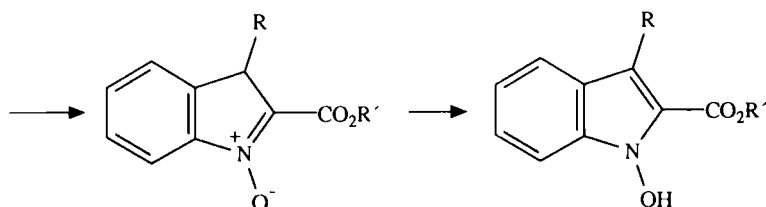
### 5. Attack of Carbanions on Nitro Groups

In 1896, Reissert (1896CB646) discovered that refluxing 2-nitrobenzylmalonic acid or the ester **295** with 33% aqueous sodium hydroxide for a short time gave the acid **297** in 80% yield. Ethyl 3-keto-2-(2-



295 R = H

296 R = CN

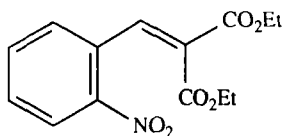


297 R = R' = H

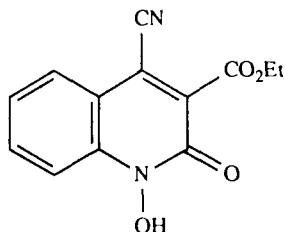
298 R = CN, R' = Et

nitrobenzyl)butyrate behaved similarly (23CB1024), and this type of synthesis has been reviewed (64QR389; 72CRV627). When warm 1% aqueous sodium carbonate was used, then partial hydrolysis of the ester group took place. The reaction must proceed as indicated through nucleophilic attack on the nitro group, followed by a type of reverse Claisen condensation. If a carbanionic center one atom further from the benzene ring can be developed, then quinoline 1-oxide formation can take place competitively; weakly basic conditions favor 1-hydroxyindole formation and the acid **297**, bearing a nitrile or carbamide group at position 3. 3-Cyano-1-hydroxy-5-methoxy-2-phenylindoles have been made by this type of synthesis (72CRV627).

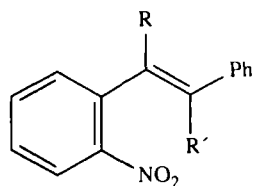
Hydrogen cyanide can also be added to 2-nitrobenzylidene derivatives, such as **299**, to give **296**, and then cyclization to **298** takes place with ethanolic sodium carbonate. The more basic potassium cyanide or hydroxide, however, converts **296** into the quinolone **300** (72CRV627). Both nitriles **301** and **302** with potassium cyanide give the indole **304** via the common intermediate **303**. If piperidine is added, 2-amino-4-cyano-3-phenylquinoline 1-oxide is the main product (60JCS3466). The indole **305** has been obtained similarly from **306** [70JCS(C)1916].



299

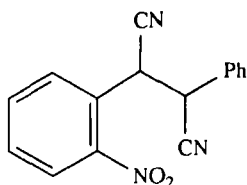


300

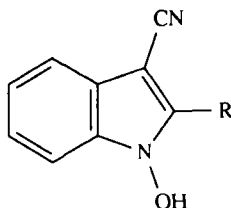


301 R = H, R' = CN

302 R = CN, R' = H

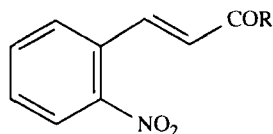


303



304 R = Ph

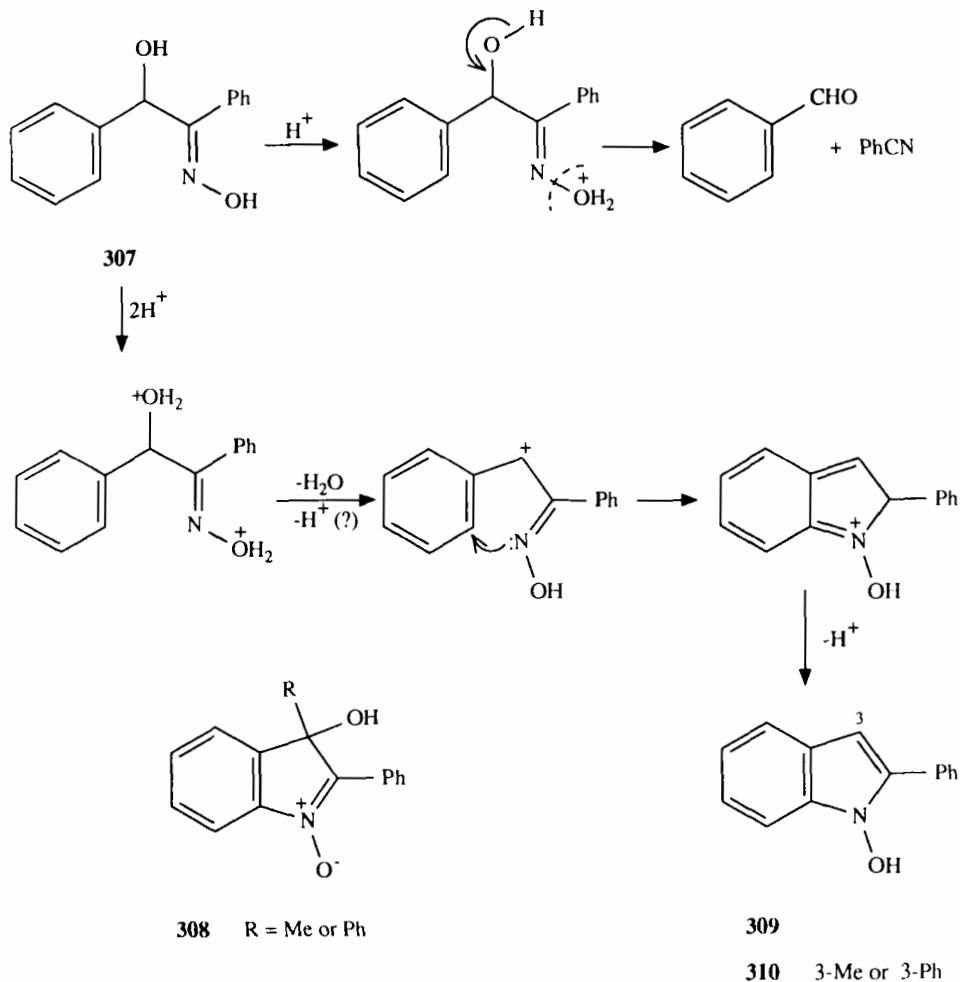
305 R = Me



306 R = Me or Ph

## 6. Benzoin Oximes and Concentrated Sulfuric Acid

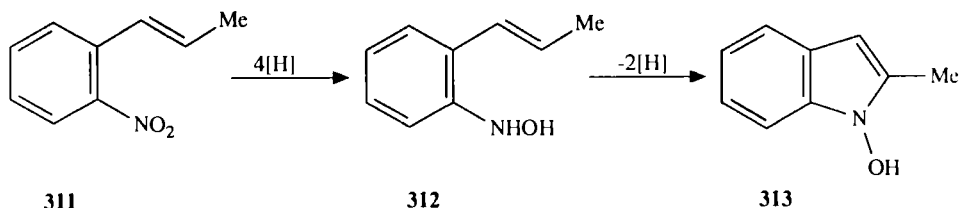
Benzoin oxime (307) with concentrated sulfuric acid gives 1-hydroxy-2-phenylindole (309) in high yield (75JOC3735). At lower concentrations and in phosphoric acid, fragmentation occurs to form benzonitrile and benzaldehyde. From the rates of cyclization in 60–100% sulfuric acid, it has been concluded (75JOC3735) that monoprotection leads to fragmentation, and diprotection leads to indole formation. Although it was originally reported (75JOC3735) that the  $\alpha$ -methyl- and  $\alpha$ -phenylbenzoin oximes gave the corresponding 1-hydroxyindoles (310), it now appears [80JCS(P2)339] that the substances described were mixtures of these 1-hydroxyindoles and the corresponding 3-hydroxy-3*H*-indole 1-oxides (308) formed by autoxidation. This could be associated with a reduction in steric strain, which would not occur on the similar oxidation of 309, or to greater activity at the 3-position due to substitution.



### 7. Oxidation of Indoles to 1-Hydroxyindoles

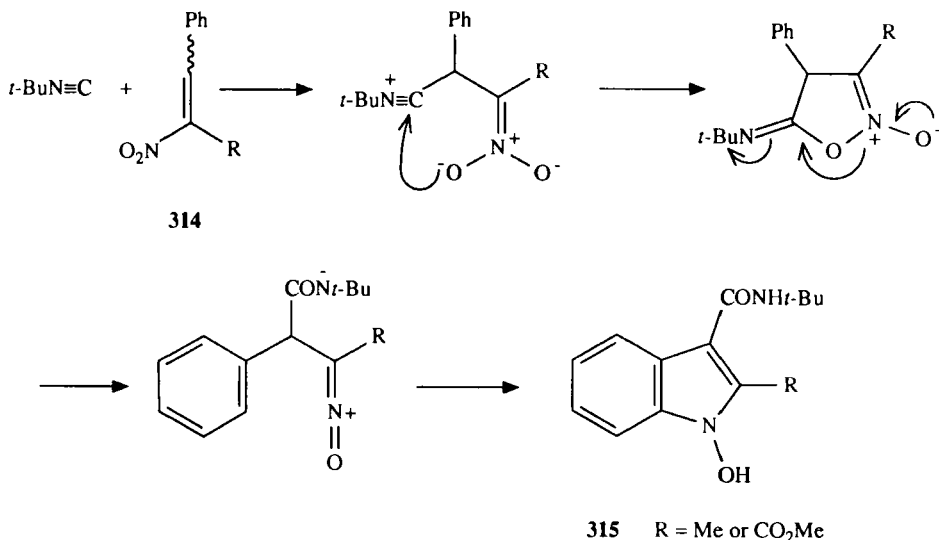
A number of claims have been made that this type of oxidation can be effected by chemical means, but all have been discounted [65M11; 68JCS(C)504] except perhaps one. 1-Hydroxy-2-phenylindole has been detected (74CC677) as an intermediate in the oxidation of 2-phenylindoline by 3-chloroperbenzoic acid to 2-phenylisatogen (**321**), but even here it is possible that N-oxidation of the indoline takes place and is followed by aromatization. The formation of a few 1-hydroxyindoles not possessing an

electron-attracting group at position 2, such as **313**, occurs when the corresponding hydroxylamine (**312**) is subjected to anodic oxidation under nitrogen. The hydroxylamine was prepared *in situ* in the same electrolysis cell by reduction of the nitro compound **311**, and no isolated yields were reported (74BSF121).



### 8. 1-Hydroxyindoles from Isocyanides

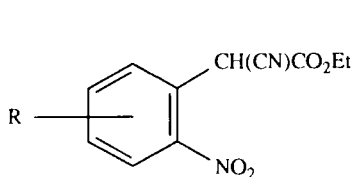
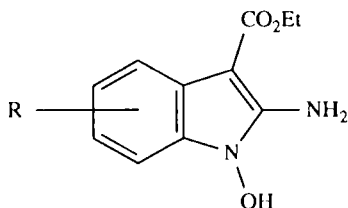
A number of indoles of type **315** have been made (80TL281; 83JOC3639) by stirring *t*-butyl and some other isocyanides in benzene or acetonitrile with various aryl nitropropenes (**314**), and the reaction is thought to proceed as indicated. 5-, 6-, and 7-Substituted and benzo[*e*]- and -[*g*]-1-hydroxyindoles have also been obtained; yields varied from 15–87%.



### 9. 1-Hydroxyindoles from Alkyl 2-Nitrophenylcyanoacetates

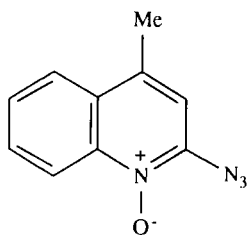
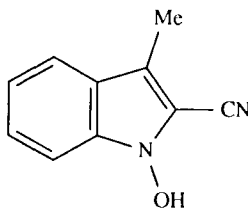
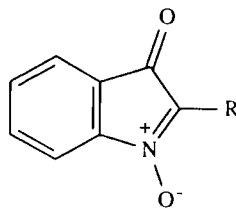
Reduction of ethyl 2-nitrophenylcyanoacetates (**316**) with zinc and acetic acid at 15–28°C gave (87JHC1145) the corresponding 2-amino-1-

hydroxyindoles (**317**); higher temperatures removed the hydroxy group, giving the corresponding *1H*-indoles.

**316****317**

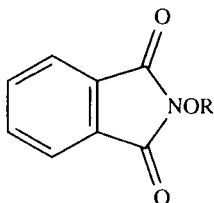
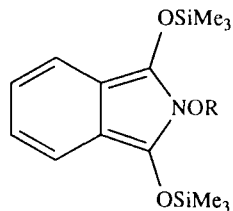
#### 10. *1-Hydroxyindoles from 2-Azidoquinoline 1-oxides*

Heating the quinoline **318** in toluene gave 44% of the indole **319** (see Section II,F for the mechanism); if the methyl group was absent, then the isatogen **320** was formed (80JOC5316).

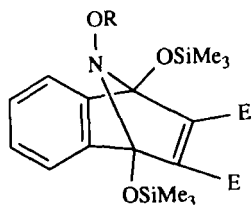
**318****319****320** R = CN**321** R = Ph

#### IV. 2-Alkyloxyisoindoles

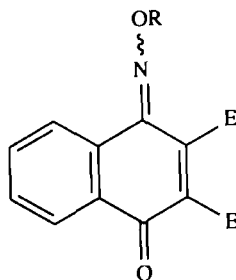
Very few compounds of this type are known, and none bear a 2-hydroxy group. The phthalimides (**322**), on cathodic reduction in anhydrous aceto-

**322**R = Me and CH<sub>2</sub>Ph**323**





324

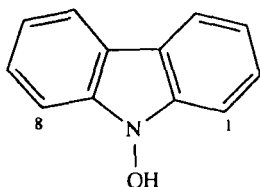


325

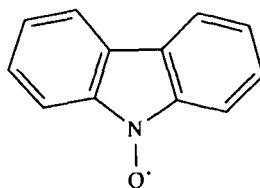
nitrile with chlorotrimethylsilane at 0°C, gave the corresponding isoindoles (**323**), which were stable in solution under an inert atmosphere. Treatment with dimethyl acetylenedicarboxylate gave a mixture of the *E*- and *Z*-quinones (**325**), probably via **324**, which could not be isolated [87ZN(B)1027].

## V. 9-Hydroxycarbazoles

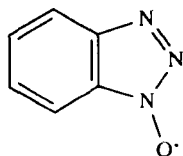
*N*-Hydroxycarbazole (**326**) was first postulated (64JOC2808) as an intermediate in the reaction of benzyne with nitrosobenzene, which gave *N*-phenylcarbazole. Later it was obtained in 1% yield from diazotized anthranilic acid and nitrosobenzene, while tetrahalogenated benzynes,



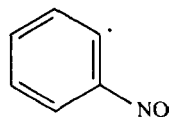
326



327



328



329

obtained in the same way, gave up to 30% of the corresponding tetrahalogenated-1-hydroxycarbazoles [74JCS(P1)2695]. Oxidation of 9-hydroxybenzotriazole by lead dioxide in benzene, presumably via **328**, **329**, and **327**, leads to some of **326** [77JCR(S)122]. The radical **327** has been detected, the 1,2,3,4-tetradeuterio derivative has been made from C<sub>6</sub>D<sub>6</sub>, and their ESR spectra have been reported (73CB2408). The photolysis of carbazole in the presence of di-*t*-butyl peroxide gave the radical **327**. Dimethyl peroxide, in contrast to the di-*t*-butyl compound which failed, gave corresponding radicals when the 1- and or 8-positions of the carbazole were substituted by *t*-butyl groups (72CB2694).

Carbazole 9-oxyl **327** has been identified from its ESR spectrum in the livers of English sole with hepatic neoplasms; it was also found in healthy fish after they had been injected with carbazole (85MI2) (see also Section III,F).

#### ACKNOWLEDGMENTS

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# Preparation of Pyrroles from Ketoximes and Acetylenes

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## I. Introduction

During the 1970s and 1980s, interest in the chemistry of pyrroles has greatly increased. Three fundamental monographs have come out (74MI1; 77MI1; 84MI1) and comprehensive reviews are being published [76S281; 80KGS1299; 84MI4, 84MI5, 84MI6, 84MI7, 84MI8, 84MI9; 85MI1; 86MI3; 87MI1; 89KGS291; 89UK]. The stream of papers dealing with diverse aspects of preparative, theoretical, and applied chemistry of pyrroles is progressively growing. This is due in part to both the isolation from natural products of a number of comparatively simple pyrrolic compounds (74MI1; 77MI1; 78MI1) including antibiotics, ferromones, and toxins and the discovery of new possibilities for pyrrole ring polypyrroles possessing metal-like electroconductivity in solar energy transformation (81JA1849, 81MI1; 82JA2032, 82MI1).

The chemistry of pyrroles also includes complex pyrrole systems, porphyrin, and phthalocyanine structures such as haemin, chlorophyll, hemoglobin, bile pigments, cytochromes, and vitamin B<sub>12</sub>.

However, since the mid 1970s, an event now called "the pyrrole renaissance" (77MI1), i.e., a revival of the chemistry of relatively simple pyrrole compounds, has taken place. The pyrrole renaissance is also facilitated by the fact that, along with the continued isolation and investigation of natural pyrroles (e.g. 81MI2, 81MI3), extended studies of their synthetic analogs are being carried out (80JHC1081), and reliable synthetic routes to key "building blocks" (pyrrole moiety carriers) and mainly simple pyrrole compounds are being developed.

It is the synthesis of simple pyrroles, especially alkyl substituted ones, that has provided the greatest difficulties, as Jones and Bean emphasize in their monograph (77MI1). Thus, of the score of reactions for pyrrole ring construction reported by Gossauer (77MI1), only a few are of preparative value, the majority being multi-stage, time-consuming, and based on starting materials difficult to obtain.

*N*-Vinylpyrroles are one of the universal types of reactive carriers of the pyrrole moiety which can be used for different purposes in organic synthesis and polymerization. However, even in the early 1970s, they were considered (74MI1) to be almost unknown and unavailable compounds. Indeed, except for the comparatively well known *N*-vinyl derivatives of

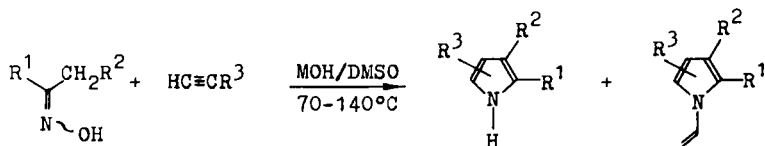
carbazole (56LA128; 60MI1; 66MI1) and indole (62USP3047583; 66MI2; 69UK829), quite different in their properties from typical pyrroles in spite of the fact they contain a pyrrole ring, other representatives of this series were only briefly mentioned in a few papers (56LA128; 62USP3047583; 71TL4321; 72T1113). This situation was unexpectedly and abruptly changed in 1970 by the discovery and subsequent systematic development of the reaction of ketoximes with acetylenes in an alkali metal hydroxide/dimethyl sulfoxide (DMSO) system leading to pyrroles and *N*-vinylpyrroles in one preparative stage and in high yield (80KGS1299; 81MI4; 84MI1). [This reaction is now called the Trofimov reaction (79KGS1567; 81KGS1412; 87MI2).] The synthesis of various *NH*-pyrroles became much easier. Previously very expensive and exotic, *N*-vinylpyrroles turned into the cheapest and most available compounds of the pyrrole series. At present they are extensively and systematically investigated by many scientific teams as promising monomers, intermediates for fine organic synthesis, and biologically active compounds.

The results of these investigations were reported in dozens of papers, monographs (81MI4, 81MI5; 84MI1), reviews [80KGS1299; 81UK248; 85MI3, 85UK1034; 86ZC41, 86ZOR1991; 87MI1; 89KGS291; 89UK275], and theses. It is quite urgent to summarize, correlate, and critically appraise the accumulated experimental data. This is the object of the present review.

## II. Experimental Conditions of the Ketoxime–Acetylene Condensation Affording Pyrroles

### A. GENERAL FEATURES OF THE REACTION

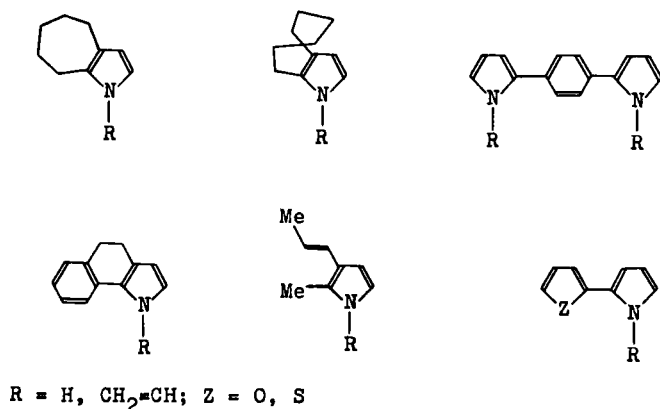
Ketoximes react with acetylenes in a strong base/DMSO system to form *NH*- and *N*-vinylpyrroles (e.g. 73MI1, 73ZOR2205; 74MI2; 75KGS360, 75MI1, 75MI2, 75MIP1; 77BRP1463228, 77GEP2543850, 78USP4077975, 78MIP1, 79MI1, 79MI2, 79MI3, 82JAP1090993).



$\text{R}^1, \text{R}^2, \text{R}^3$  - H, organic or heteroorganic radicals;

M - alkali metal

The reaction allows diverse *NH*- and *N*-vinylpyrroles to be prepared. The yields depend on the structure of the reactants, but in the case of simple ketoximes and unsubstituted acetylenes, they are fairly stable, amounting to 70–95% under optimal conditions. Along with simple alkyl- and aryl-substituted pyrroles, compounds which previously could be obtained by conventional methods only with difficulty, if at all, now become readily available. These are, for example, annelated pyrroles from oximes of cyclohexanone, suberone (75KGS1225; 76MIP1), macrocyclic ketones [90IZV(ip)], tetralone (78ZOR1119), as well as various alkenyl, furyl, and thienyl pyrroles and the like (77KGS1136; 78ZOR2628; 79IZV2372; 82TL5063, 82ZOR2620).



The principle and determining advantage of this reaction is that it is based on ketones, which are cheap and accessible compounds. Besides, there appeared a possibility for previously almost inaccessible *N*-vinylpyrroles to be readily synthesized.

The pyrrolization of ketoximes with acetylene proceeds smoothly at 70–140°C, in most cases at 80–100°C (73ZOR2205; 77BRP1463228, 77GEP2543850, 78MIP1, 78USP4077975; 79KGS197, 79ZOR602; 82JAP1090993). When the reaction is carried out on a large scale, heating the reactants to this temperature is sometimes enough to start a mild exothermal process further, thermally regulated by mere acetylene feeding.

The synthetic procedure is very simple to perform: acetylene is passed under atmospheric pressure into a heated solution of reactants upon stirring. The reaction proceeds to completion over 3–8 hr on average. Naturally, autoclave can be used, since, under pressure, the process comes to an end more quickly.

## B. SUPER BASES AS SPECIFIC CATALYSTS

The reaction is specifically catalyzed by a superbase pair: strong base/DMSO (73MI1; 79MI1, 79MI2, 79MI3; 81UK248; 86ZC41, 86ZOR1991). Usually an alkali metal hydroxide is employed as a strong base, although specially prepared oximates, alkoxides, and quaternary ammonium bases are also active (73MI1, 73ZOR2205; 74MI2; 75MI1, 75MI2, 75MIP1; 77BRP1463228, 77GEP2543850; 78MIP1, 78USP4077975, 78ZOR1119, 78ZOR2628; 79MI1, 79MI2, 79MI3).

Superbases consist of a strong base and a complexing agent capable of binding the cation, thus "stripping" the conjugated anion in a medium that is poorly solvating anions (79MI4; 81UK248; 86ZC41, 86ZOR1991). This system can be obtained from linear and cyclic glycol ethers, macrocyclic polyethers (crown ethers), and dipolar aprotic (nonhydroxylic) solvents, i.e., organic sulfoxides, sulfones, phosphorylamides, phosphine oxides, and liquid ammonia.

The basicity of sodium methylate, for example, in 95% DMSO is higher by seven orders of magnitude than that in pure methanol (62T917):

NaOCH <sub>3</sub> , 0.025M	
Solvent	Acidity function, H <sub>0</sub>
Methanol	12.2
95% DMSO + 5% methanol	19.4

The increase in basicity is most pronounced in the region of extremely high concentrations of dipolar aprotic solvent. Thus, tetramethylammonium hydroxide in 99.5% aqueous DMSO is more basic by 14 orders than in pure water (67CJ911).

The superbasicity of the KOH/DMSO system as a first approximation is due to the separation of the base ion-pair (79CJC538) and the formation of a highly basic and poorly solvated dimethyl anion (79MI4; 81UK248; 86ZC41, 86ZOR1991). In the general case, account should be taken of cooperative effects of changes in the dielectric constant of the medium, hydrogen bonding, water activity, and dispersion interactions, as well as of changes in the structure of water and the extent of ion hydration (67CJC911, 67IC528; 76JOC1614).

Superbases are also likely to be formed at interface under the conditions of phase-transfer catalysis (77AG521, 77UK2174; 80MI1; 83MI1; 86ZOR489) when a highly concentrated or solid alkali (or other strong base) is used where the anion transfer is effected by a bulky organophilic cation incapable of forming a contact ion pair.

Synergism in the action of bases, i.e., the activation of one base by the other, is a real phenomenon finding an ever extending and successful application in preparative organic chemistry (78MI2).

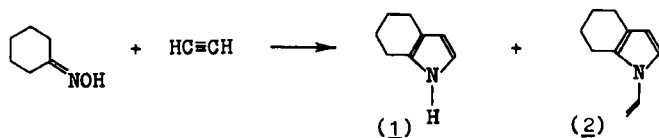
There seems to be a certain analogy between the activation of one base via the formation of mixed complexes with the other base and the activation of a base as a result of solvation of its cation by a dipolar aprotic solvent. In real systems, these two activation routes are interrelated and take place much more frequently than it may appear at first glance, facts which are not commonly taken into consideration in interpreting the reaction mechanisms involving bases. Thus, during the synthesis of pyrroles in the  $\text{KOH}/\text{R}_2\text{C}=\text{NOH}/\text{HC}\equiv\text{CH}/\text{DMSO}$  system there can simultaneously be present several bases, namely,  $\text{KOH}$ ,  $\text{R}_2\text{C}=\text{NOK}$  (oximate),  $\text{HC}\equiv\text{CK}$  (acetylide), and  $\text{MeSOCH}_2\text{K}$  (dimethylpotassium), which should give the whole gamut of complex bases in various combinations.

Acetylene in superbases  $\text{MOH}/\text{DMSO}$  systems can be activated in several ways: (i) H-bonding with solvent; (ii) formation of complexes with  $\text{MOH}$  (Tedeschi complexes) (41GEP712742; 48USP2455058; 63JOC2480; 65JOC3045; 68MI1; 70MI1; 82MI2); (iii) ionization and formation of acetylides (87IZV2777; 88IZV1335, 88IZV1339); and (iv) insertion into the inner solvation sphere of the alkali metal cation (82IZV891, 82IZV1474, 82IZV1477).

*Ab initio* quantum chemical calculations show the existence of bonding interactions between acetylene and an alkali metal cation, the complex formed being a nonclassical bridged structure with the electron density transferred to a large extent onto the cation (82IZV891, 82IZV1474, 82IZV1477).

This reduces the energy of low-lying vacant molecular orbitals of free acetylene in this complex, as compared with analogous orbitals of free acetylene, and consequently the triple bond becomes more accessible to nucleophilic attack. As for nucleophiles, they become supernucleophiles in superbases media because of a sharp increase in their energy (76G817; 77APO133).

The catalytic function of the  $\text{KOH}/\text{DMSO}$  system in heterocyclization of ketoximes with acetylene is manifested when mixed  $\text{DMSO}/\text{dioxane}$  solvent is used. The results obtained for the reaction of cyclohexanone



SCHEME 1

TABLE I  
DEPENDENCE OF THE YIELD OF 4,5,6,7-TETRAHYDROINDOLE 1  
AND ITS *N*-VINYL DERIVATIVE (2) ON THE COMPOSITION  
OF DMSO/DIOXANE MIXTURE<sup>a</sup>

DMSO content, mass parts	Total yield <sup>b</sup> of indoles 1 and 2 (%)		
	Based on oxime taken	Based on oxime consumed	Indole 2 content of the mixture <sup>b</sup> (%)
0.00	0	0	0
0.05	10	30	trace amount
0.14	35	67	trace amount
0.32	40	82	10
0.50	53	87	80
1.00	77	93	99.5

<sup>a</sup> 120°C, 2 hr, 20 % KOH of the mass, excess C<sub>2</sub>H<sub>2</sub> under a pressure of 16 atm. From reference (78ZOR1733). See also Scheme 1.

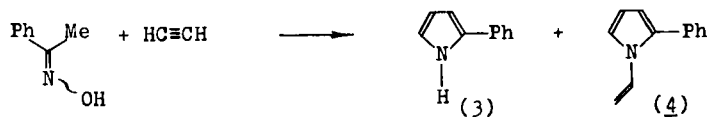
<sup>b</sup> From GLC data.

oxime with acetylene (81ZOR1977) (see Scheme 1) are given in Table I.

It can be seen that the reaction takes place when DMSO is added to the dioxane solution in as small amounts as 5–10%. Varying the DMSO concentration makes it possible to carry out the reaction selectively, which means that either 4,5,6,7-tetrahydroindole (1) (with a small DMSO content) or 1-vinyl-4,5,6,7-tetrahydroindole (2) (in pure DMSO) can be obtained.

Analogous conclusions have been drawn in studying the reaction of acetophenone oxime with acetylene (Scheme 2) leading to 2-phenylpyrrole (3) and 2-phenyl-1-vinylpyrrole (4) (78ZOR1733).

As seen from Table II, the decrease in the DMSO content of mixtures with dioxane drastically reduces the yield of 2-phenyl-1-vinylpyrrole. Varying the DMSO concentration makes it possible to obtain selectively either 2-phenylpyrrole or its *N*-vinyl derivative.



SCHEME 2



TABLE II  
EFFECT OF DMSO/DIOXANE MIXTURE ON YIELD OF  
2-PHENYLPYRROLE (3) AND 2-PHENYL-1-VINYLPYRROLE (4)<sup>a</sup>

DMSO content, vol. parts	Yield (%)	
	Pyrrole 3	Pyrrole 4
0.2	27	trace amounts
0.4	50	23
0.6	45	25
1.0	trace amounts	71

<sup>a</sup> 100°C, 3 hr, 30 % KOH of the oxime mass, excess C<sub>2</sub>H<sub>2</sub> under a pressure of 12 atm. From reference (78ZOR1733). See also Scheme 2.

### C. EFFECTS OF THE SUPERBASE COMPOSITION

#### 1. Nature and Content of a Strong Base

Alkali metal hydroxides MOH (M = Li, Na, K, Rb, Cs) and tetrabutylammonium hydroxide were used as a strong base for the synthesis of pyrroles from ketoximes (78ZOR1733; 81ZOR1977).

The dependence of the catalytic activity upon the nature of the hydroxide cation (Tables III and IV) was studied using the same reactions of cyclohexanone and acetophenone oximes with acetylene as an example

TABLE III  
EFFECT OF ALKALI METAL HYDROXIDE (MOH) CATION ON  
YIELD OF TETRAHYDROINDOLE (1) AND (2)<sup>a</sup>

Metal	Total yield <sup>b</sup> of product (%)	Composition of mixture <sup>b</sup> (%)		
		Oxime	Indole 1	Indole 2
Li	99	90	10	traces
Na	97	80	20	traces
K	93	traces	traces	100
Rb	81	traces	100	traces
Cs	84	traces	30	70
Bu <sub>4</sub> N	70	traces	100	traces

<sup>a</sup> 120°C, 2 hr, 20 mol % MOH, DMSO, excess C<sub>2</sub>H<sub>2</sub> under a pressure of 16 atm. From reference (81ZOR1977). See also Scheme 1.

<sup>b</sup> From GLC data.

TABLE IV  
EFFECT OF ALKALI METAL HYDROXIDE CATION  
ON YIELD OF 2-PHENYLPYRROLE (3) AND  
2-PHENYL-1-VINYLPYRROLE (4)<sup>a</sup>

Metal	Yield (%)	
	Pyrrole 3	Pyrrole 4
Li	66	traces
Na	traces	57
K	traces	71
Rb	traces	64
Cs	traces	66

<sup>a</sup> 100°C, 3 hr, 30 % MOH, DMSO, excess C<sub>2</sub>H<sub>2</sub> under a pressure of 12 atm. From reference (78ZOR1733). See also Scheme 2.

(Schemes 1 and 2). A distinct dependence of the MOH/DMSO catalytic activity on the nature of cation was observed (78ZOR1733; 79KGS197, 79MI2). In general, it is raised with increasing cation atomic number, however, the best yields under the conditions chosen were achieved with  $M = K$ :



Although true for many oximes of aliphatic and alicyclic ketones, the previous sequence is not absolute and can change depending on the reaction conditions and ketoxime type. Tetrabutylammonium hydroxide, for instance, which catalyzes fairly actively in the synthesis of 4,5,6,7-tetrahydroindole from cyclohexanon oxime and acetylene (79KGS197), turned out to be nearly inert with alkyl aryl ketoximes (78ZOR1733).

Calcium hydroxide is inactive under conditions (100°C, 3 hr) where the reaction of acetophenone oxime with acetylene is well catalyzed by alkali metal hydroxides in amounts of 10–30% relative to the oxime mass (78ZOR1733). Tetrabutylammonium hydroxide produces a weak catalytic effect on this reaction only under more rigid conditions (120°C). Potassium, zinc, and cadmium acetates as well as zinc, copper(I,II), and cobalt chlorides do not show any catalytic activity (the starting acetophenone oxime returns practically unconsumed), though the cations of the previously mentioned salts have long been known (56LA128; 72MI1, 72MI2; 76KGS516) as specific catalysts of direct vinylation of *NH*-heterocycles by acetylene. From Tables III and IV, it is evident that alkali metal hydroxides differ in not only their activity, but in the selectivity of action. Thus, LiOH catalyzes selectively in the reaction of building up the

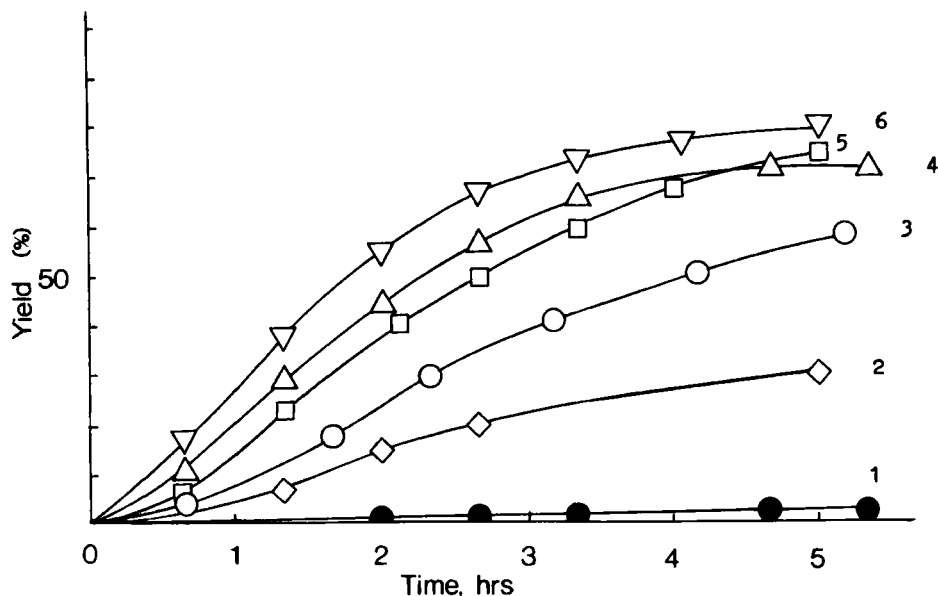


FIG. 1. Effect of alkali metal hydroxides (MOH) on the yield of 2-phenylpyrrole [89KGS291]: 1, LiOH (anhydrous); 2, NaOH (1 % H<sub>2</sub>O); 3, KOH (15 % H<sub>2</sub>O); 4, KOH (calcined); 5, RbOH (13 % H<sub>2</sub>O); 6, CsOH (7 % H<sub>2</sub>O). Reaction conditions: DMSO, 96°C, P<sub>C<sub>2</sub>H<sub>2</sub></sub>, 720 mm Hg, conc. of MOH and acetophenone oxime 0.5 mol/L.

pyrrole ring from alkyl aryl ketoximes (78KGS489, 78MIP2, 78ZOR1733, 78ZOR2182) and is almost inactive at the stage of vinylation of the pyrrole. At the same time, for alicyclic ketoximes, LiOH is ineffective at both stages (81ZOR1977), the building up of the pyrrole fragment in this case being more selectively accelerated with rubidium and tetrabutylammonium hydroxides (79KGS197; 81ZOR1977).

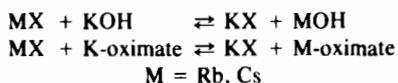
A small decrease in the yield of 2-phenyl-1-vinylpyrrole (4) when RbOH and CsOH are used as the catalyst instead of KOH is a result of enhanced resinification (78ZOR1733). Large differences in the catalytic activity of alkali metal hydroxides with respect to the reaction of acetophenoneoxime with acetylene (Scheme 2) in the MOH/DMSO system at 96°C and under atmospheric pressure were confirmed in studying the kinetics of this reaction (Fig. 1). According to these data the catalytic activity increases in the following sequence [89KGS770]:



A slightly reduced rate of heterocyclization in the presence of RbOH as compared with that of KOH (Fig. 1, curves 4 and 5) is explained by a higher water content in the former (13%). The kinetic curve of heterocyclization

derived with KOH containing about 15% water (Fig. 1, curve 3) lies considerably lower than curves 4 and 5. This illustrates the inhibiting effect of water in this reaction (80KGS1299; 84MI1). The most active catalyst in this case is cesium hydroxide in spite of the presence of about 7% of water. Lithium hydroxide (Fig. 1, curve 1), even free of water, catalyzes the reaction considerably less effectively than sodium hydroxide with a 1% water content (Fig. 1, curve 2).

Since rubidium and cesium hydroxides are most active in catalyzing the conversion of ketoxime to the corresponding pyrrole (3) [89KGS770] it might be supposed that the additives of salts of these metals to the KOH/DMSO system would increase the catalytic activity of the latter because of exchange processes:



However, of all the salts tested (RbCl, CsF,  $\text{Cs}_2\text{CO}_3$ ; 0.2 mol per 1 mol KOH), only cesium fluoride shows a perceptible catalytic effect (yield gain up to 8%) at the stage of pyrrole formation for only the first three hours (Fig. 2, curve 3). The observed effect can be explained in terms of poor solubility of potassium fluoride in DMSO (86MI1).

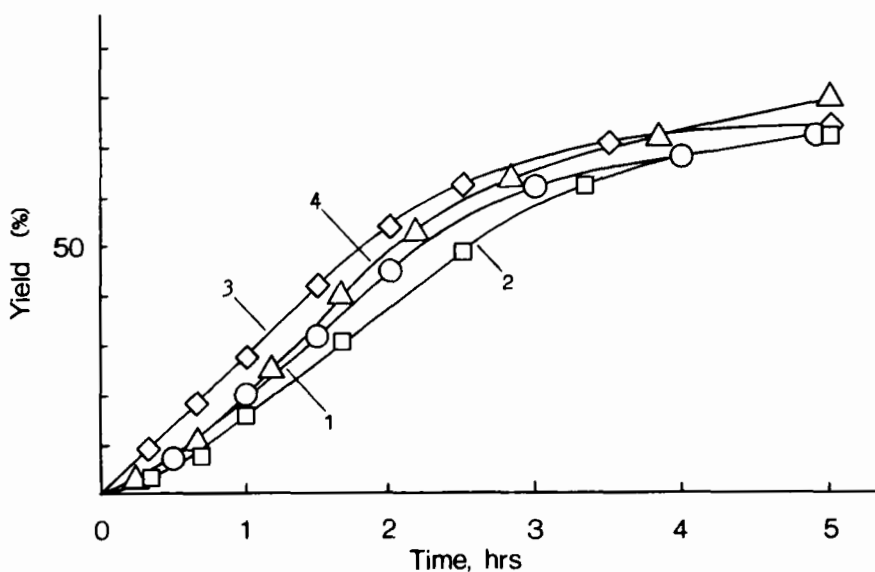
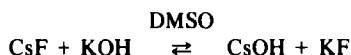
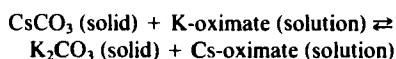


FIG. 2. Effect of salt additives (0.2 mol per 1 mol of KOH) on the yield of 2-phenylpyrrole [89KGS291]: 1, no additive; 2, RbCl; 3, CsF; 4,  $\text{Cs}_2\text{CO}_3$ . Reaction conditions: see Fig. 1.



Rubidium chloride even slows the reaction, this is especially well seen within a time span of 1–3 hr after the start of the process (Fig. 2, curve 2). In this case the normal salt effect is likely to prevail over the effect of oximate ion pair separation due to substitution of the potassium cation by the rubidium cation. The addition of cesium carbonate during the first 1.5 hr does not much affect the rate of the formation of 2-phenylpyrrole. The accelerating effect of these additives becomes evident only 2 hr after the beginning of the reaction and gradually increases (5 hr later the yield gain of pyrrole is 7% as compared with a standard run, Fig. 2, curve 4) which seems to result from a slow rate of heterophase exchange process:



The effect of the KOH content of the reaction mixture upon the yield of 3-methyl-2-phenyl-1-vinylpyrrole from propiophenone oxime and acetylene (100°C, 3 hr) is expressed as follows (78ZOR1733)

KOH (%)	5	10	15	20	30	100
Yield (%)	7	23	39	50	76	68

A zinc powder additive to KOH (1:3 by mass) obviously allows the reaction temperature to be slightly reduced or the duration of synthesis to be shortened (Scheme 2), a good yield of 2-phenyl-1-vinylpyrrole (3) remaining unchanged (Table V). However, the effect of this promoting

TABLE V  
SYNTHESIS OF 2-PHENYLPYRROLE AND 2-PHENYL-  
1-VINYLPYRROLES IN THE PRESENCE OF A KOH-Zn SYSTEM<sup>a</sup>

Temp. °C	Time (hr)	Yield (%)	
		2-phenylpyrrole	2-phenyl-1-vinyl-pyrrole
70	2	12	5
75	2	39	7
80–85	2	45	17
100	1	traces	70
100	0.5	traces	63

<sup>a</sup> 1.5 g KOH, 0.5 g Zn, 50 ml DMSO, 6.75 g acetophenone oxime, excess C<sub>2</sub>H<sub>2</sub> under a pressure of 12 atm. From reference (78ZOR1733). See also Scheme 2.

additive is not as unambiguous as that during vinylation of carbazole (60MI1, 66MI1).

A much more efficient means of promoting the reaction is variation of the KOH content of the reaction mixture. This was convincingly shown for the conversion of cyclohexanone oxime to 4,5,6,7-tetrahydroindole (1) and its *N*-vinyl derivative in the reaction with acetylene in KOH/DMSO (Scheme 1) (81ZOR 1977). At a moderate temperature (100°C), an increase in the KOH content (up to an equimolar ratio to the oxime) enhances the yield of 1-vinyl-4,5,6,7-tetrahydroindole (Table VI). Under more severe conditions (120°C) the alkali starts to accelerate side processes as a consequence of which an inverse dependence of the yield of 1-vinyl-4,5,6,7-tetrahydroindole upon the content of base is observed (cf. Table VI).

In general, the reaction rate increases with the strong base content of the reaction mixture. At the same time, good preparative results can also be obtained with extra stoichiometric excess (nearly 10-fold) of the base with respect to ketoxime (80KGS1299; 84MI1). The optimal ketoxime/alkali ratio, however, is normally close to equimolar.

As far as the different catalytic activity of alkali metal hydroxides with different cations is concerned, this effect is far from being unique for the given reaction since it is observed in all base-catalyzed processes with the participation of alkalies: in the reaction of vinylation (59MI1; 66MI1; 68UK2070; 81MI4, 81UK248), nucleophilic substitution and elimination (e.g. 78MI3), the Favorsky reaction (67MI1), in the synthesis of divinyl

TABLE VI  
DEPENDENCE OF TETRAHYDROINDOLES YIELD (1,2) FROM CYCLOHEXANONE OXIME AND ACETYLENE ON KOH CONCENTRATION<sup>a</sup>

KOH <sup>c</sup>	Temp. (°C)	Time (hr)	Product yield (%)	Composition of product mixture <sup>b</sup> (%)		
				Oxime	Indole 1	Indole 2
30	100	3	95	10	65	35
40	100	3	95	traces	55	45
50	100	3	93	traces	40	60
100	100	3	90	no traces		100
30	120	1	93	traces	40	60
40	120	1	91	traces	30	70
50	120	1	93	no traces		100
100	120	1	60	no traces		100

<sup>a</sup> 50 ml DMSO, 1 L autoclave, C<sub>2</sub>H<sub>2</sub> initial pressure 16 atm. From reference (78ZOR1733). See also Scheme 1.

<sup>b</sup> From GLC data.

<sup>c</sup> Mol. % relative to oxime.

sulfide from acetylene and alkali metal sulfides (83MI2), cyclization of cyanoacetylenic alcohols (80IZV1349), etc. Thus, in the course of vinylation of 2-ethoxyethanol with acetylene in the presence of various hydroxides, the following relative reaction rates were observed (59MI1; 66MI1)

PhCH <sub>2</sub> NMeOH	0.00
LiOH	0.10
NaOH	0.76
KOH	1.00
RbOH	0.83

This order of base activity corresponds almost exactly to that observed in the formation of pyrroles from ketoximes and acetylene, evidently for the same causes. The failure of trimethylbenzylammonium hydroxide to catalyze the reaction of vinylation is believed (59MI1; 66MI1) to be caused by its lack of coordination. Along with inhibition of the reaction with water, pyridine, *o*-phenanthroline, and diketones, this indicates the reaction occurs by complex ionic mechanisms in which the participation of the complex ion as an intermediate is possible.

According to *ab initio* calculations (82IZV1477) in complexes of acetylene with alkali metal cations (see also Section II.B), the lowest energy belongs to vacant *2s* and *2p* atomic orbitals of the Li<sup>+</sup> cation, which show comparatively small splitting. Vacant *4s* and *4p* atomic orbitals of the cation K<sup>+</sup> lie somewhat higher, but analogous to those of Li, they remain below the lowest vacant molecular orbital (LVMO) of acetylene. Vacant *3s* and *3p* atomic orbitals of the Na<sup>+</sup> cation show positive energy values, *3p*-AO lying higher than the LVMO of the acetylene molecule.

The energy values (a.u.) of the lowest vacant orbitals of alkali metal cations in complexes with acetylene are as follows (82IZV1477)

Orbital	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>
<i>s</i>	-0.1790	0.1269	-0.0596
<i>p</i>	-0.0958	0.4326	0.1233

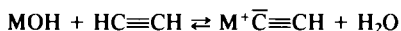
This relative arrangement of cation vacant orbitals corresponds to the drop in orbital interaction energy in the series of complexes C<sub>2</sub>H<sub>2</sub>Li<sup>+</sup> > C<sub>2</sub>H<sub>2</sub>K<sup>+</sup> > C<sub>2</sub>H<sub>2</sub>Na<sup>+</sup>.

So, the C<sub>2</sub>H<sub>2</sub>Na<sup>+</sup> and C<sub>2</sub>H<sub>2</sub>K<sup>+</sup> complexes are of different nature (cf. Section II.B). This is confirmed by analysis of the composition of binding molecular orbitals by analysis of the composition of binding molecular orbitals of these complexes. The contribution of cation atomic orbitals to

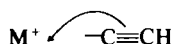
these MOs decreases in the order  $\text{Li}^+ > \text{K}^+ > \text{Na}^+$ . Correspondingly, the contribution of electrostatic interaction to complexation energy in going from  $\text{Na}^+$  to  $\text{K}^+$  decreases more abruptly than in going from  $\text{Li}^+$  to  $\text{Na}^+$ .

In solutions the energy of cation solvation decreases in the order  $\text{Li}^+ > \text{Na}^+ > \text{K}^+$ , so their ability for complexing with acetylene should change in favor of potassium to an even greater extent. With only semi-quantitative data available (yields of pyrroles), it is not possible to exactly establish the reason for the different catalytic activity of bases in this reaction.

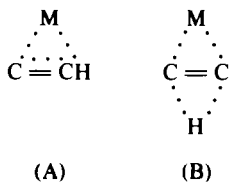
Discussing the mechanisms of nucleophilic reactions involving a  $\text{C}\equiv\text{C}$  group, due account should be taken of the fact that acetylenes are fairly strong  $\text{C}-\text{H}$  acids, and so in superbase media, they should be ionized considerably:



Evidently in acetylides of various metals, the  $\pi$ -system is polarized in a different way depending on the electronegativity and structure of the electron shell of the cation. As known (74MI3), those cations with low vacant  $d$ -orbitals can interact with the acetylide ion not only electrostatically, but by a  $\pi$ - $d$  bonding mechanism as well:



This suggests that the more the contribution from this interaction, the more bare the carbon nuclei [cf. structures (A) and (B)] and the more the triple bond would be subjected to nucleophilic attack.



Nonempirical quantum-chemical calculations of acetylide molecules support the ready displacement of alkali metal cations to the bridge position (87IZV2777; 88IZV1335, 88IZV1339). This naturally leads to the conclusion that the polarization and deformation of the  $\pi$ -electronic shell of acetylene must depend on the atomic number of the cation attached to the acetylene anion. However, the acetylene activation in the reaction with ketoximes via acetylides suggests nucleophile attack at a carbanion-like complex, which is of course a weak point of the hypothesis. Nevertheless, the electrophilic assistance from the alkali metal cation ( $\text{Na}^+$ ) to the



nucleophilic addition of the fluoride ion to acetylene is confirmed by nonempirical quantum-chemical calculations (78HCA2538).

Since, in transition metal complexes, the carbene (vinylidene) form of acetylene is often stabilized, it is quite possible that in the presence of alkali metal cation this form also becomes more stable and makes a certain contribution to activation of the triple bond.

## 2. Solvent and Complexing Components

The reaction takes place only in strongly polar nonhydroxilic solvents which form when coupled with a strong base—a superbase medium, DMSO being the best of all the solvents investigated (Table VII) (78ZOR1733, 81ZOR1977).

Analyzing the data of Table VII, obtained for pyrrolization of cyclohexanone oxime (Scheme 1) under an acetylene pressure of 16 atm, concluded that the solvent effect includes not only a change in the acetylene solubility in the reaction mixture [at the above pressure DMSO dissolves 1.3–1.5 times as much acetylene as HMPA does (69MI1)], but also includes a change in the medium polarity [the dipole moments of these two solvents differ slightly (71MI1)]. The solvent effect seems to be conditioned by differences in a specific solvation which activates reactants and, in this case, resembles catalysis.

Similar results have been obtained in studying the reaction of acetophenone oxime with acetylene (Scheme 2): 2-phenylpyrroles **3** and **4** are formed only in DMSO. When the synthesis is performed in sulfolane, only trace amounts of the pyrroles are observed, whereas in dimethylfor-

TABLE VII  
EFFECT OF SOLVENT ON TETRAHYDROINDOLES YIELD (**1,2**)<sup>a</sup>

Solvent	Composition of mixture <sup>b</sup> (%)		
	Oxime	Indole 1	Indole 2
DMSO	traces	traces	100
Dibutylsulfoxide	traces	traces	100
Hexamethylphosphoric triamide (HMPA)	20	50	30
Tetrahydrothiophene-1,1-dioxide (Sulfolane)	40	48	12
Dioxane	100	none	none
Benzene	100	none	none
Methanol	100	none	none

<sup>a</sup> 140°C, 10 % KOH of cyclohexanon oxime mass, 1 hr, excess C<sub>2</sub>H<sub>2</sub> under initial pressure of 16 atm. From reference (81ZOR1977). See also Scheme 1.

<sup>b</sup> From GLC data.

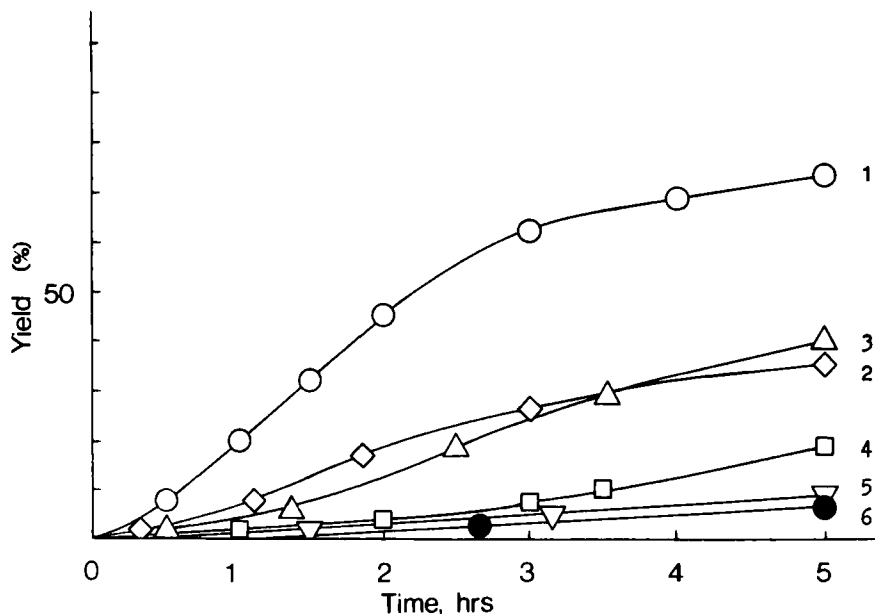


FIG. 3. Solvent effect on the yield of 2-phenylpyrrole [89KGS291]: 1, DMSO; 2, HMPA; 3, 1-methyl-2-pyrrolidone; 4, sulfolane; 5, PEG; 6, tetramethyl urea. Catalyst KOH (0.5 mol/L), for other reaction conditions see Fig. 1.

namide (DMF), HMPA, dioxane, benzene, and methanol, the reaction does not occur at all (100°C, 3 hr, 30% KOH, excess  $C_2H_2$  under initial pressure of 12 atm).

So in comparison with DMSO, other nonhydroxylic polar solvents such as HMPA and sulfolane form systems rather less active in catalyzing the synthesis of pyrroles from ketoximes and acetylene. At least, alternative routes based on their application have not been well developed and remain of less preparative importance. In solvents such as ethers, alcohols, and hydrocarbons, the reaction fails to occur (80KGS1299; 84MI1).

Figure 3 presents kinetic curves for the formation of 2-phenylpyrrole (Scheme 2) at 96°C and atmospheric  $C_2H_2$  pressure in various solvents such as DMSO, HMPA, 1-methyl-2-pyrrolidone, sulfolane, polyethylenglycol (PEG) with  $M_n = 1000$ , and tetramethylurea [89KGS770]. DMSO is confirmed to possess a specific catalytic effect in this reaction, which is much superior to that of HMPA, 1-methyl-2-pyrrolidone, and tetramethylurea. According to their capability to catalyze the formation of 2-phenylpyrrole from acetophenone oxime and acetylene, the solvents under consideration are arranged in the following order: DMSO > HMPA  $\approx$  1-methyl-2-pyrrolidone > sulfolane > PEG > tetra-

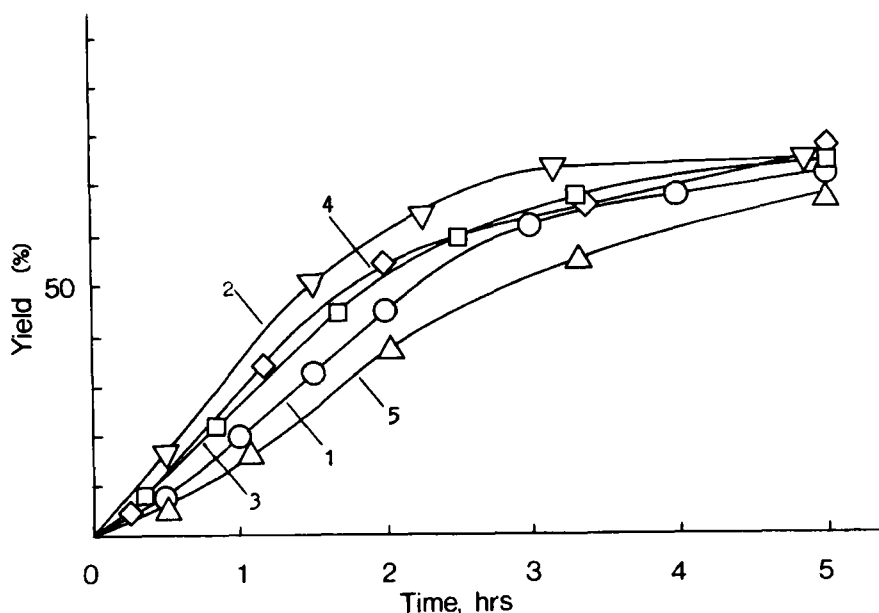


FIG. 4. Effect of complexing components (1 mol per 1 mol of KOH) on the yield of 2-phenylpyrrole [89KGS291]: 1, no additive; 2, diethyl ether of diethylene glycol; 3, divinyl ether of diethylene glycol; 4, dibenzo-18-crown-6; 5, PEG (0.16 mol per 1 mol of KOH). Reaction conditions: see Fig. 1.

methylurea. Hydrazinehydrate and DMF produce no catalytic effect under the same conditions, the latter solvent being evidently converted into potassium formate.

In the synthesis of 2-phenylpyrrole (Scheme 2), with the aim to increase the KOH/DMSO basicity, use was made of additives capable of chelating the potassium cation, such as dibenzo-18-crown-6, diethyleneglycol diethyl ether, diethyleneglycol divinyl ether in an amount of 1 mol, and PEG in an amount of 0.16 mol per 1 mol KOH. As seen from Fig. 4, all the additives with the exception of PEG accelerate pyrrole formation. The pyrrole yield in 1.5–2 hr increases by 8–15% as compared to a routine run. Further, the effect of additive is levelled. The PEG additive produces the inhibiting effect seemingly due to damping of the medium basicity by the hydroxyl groups and to competing vinylation [89KGS770].

In an aqueous medium, acetylene and ketoximes react in quite a different manner to form pyridines instead of pyrroles (75KGS1427, 75MI3). Thus, acetone oxime gives a symmetric collidine (75KGS1427), whereas cyclohexanone oxime affords 6-methyl-1,2,3,4,7,8,9,10-octa-

hydrophenanthridine (80KGS1299; 84MI1). The reaction may occur with the acetylene directly obtained in an autoclave from calcium carbide.

According to the data of preliminary tests (75KGS1427, 75MI3; 80KGS1299; 84MI1), the yields of pyridines are far from good (about 10% when  $\text{CaC}_2$  is used and 20–30% with pure acetylene), however, this rather promising reaction has not yet been optimized (cf. Section III.F).

In an  $\text{H}_2\text{O}/\text{DMSO}$  medium (1 : 2 by volume) tertiary acetylenic alcohols are formed from ketoximes and acetylene in yields of up to 50% (76ZOR1180), i.e., in this case the authors encountered an analog of the Favorsky reaction (cf. Section III.G).

Recently a new catalytic system,  $\text{KCH}_2\text{P}(\text{O})(\text{NMe}_2)_2$  dissolved in  $\text{CH}_3\text{P}(\text{O})(\text{NMe}_2)_2$  (tetramethyldiamide of methylphosphonic acid) has been suggested (76ZOR1180) for anionic organic reactions. In the authors' opinion, owing to its protophilicity and stability this system is superior to the DMSO anchored catalytic system. However, the efficiency of this superbase in the synthesis of pyrroles from ketoximes and acetylene has not been checked because of poor accessibility of tetramethyldiamide of methylphosphonic acid (diaphos). The latter does not seem to be able to compete with DMSO, a product of simple oxidation of dimethyl sulfide, a pulp-and-paper industry waste. Nevertheless, if this system proves to be more efficient in the synthesis of pyrroles, it could find application in cases where it is required to convert particularly expensive and inaccessible or poorly reactive ketoximes into pyrroles. It is not reasonable, of course, to use for this purpose a specially prepared potassium derivative of diaphos, since Eq. (1) should nearly completely be displaced to the right, i.e., towards the formation of potassium oximate. Therefore, as with DMSO, it is more efficient to employ alkali metal hydroxides.



Here it is also appropriate to discuss Eq. (2), which also should mainly be shifted towards DMSO.



In this case, however, account should be taken of a large energy of KOH hydration and normally a very high KOH content in the synthesis of pyrroles as well as the ability of DMSO to form strong complexes with water (64JPC3392; 78MI3). All these factors reduce the activity of water in the system and promote the equilibrium to be shifted towards the dimsyl anion.

It has been shown that the acidity function value of saturated solutions of alkali metal hydroxides ( $\text{MOH}$ ,  $\text{M} = \text{Li}, \text{Na}, \text{K}$ ) in DMSO varies from

20.5 to 30.5 on going from LiOH to KOH (86IZV751). This strong dependence of the basicity of the MOH/DMSO system upon the cation nature is a consequence of ion-pair interaction, which increases with decreasing cation radius and different drying ability of excess alkali metal hydroxides. Thus the KOH/DMSO pair is an example of superbase medium, simplest in preparation and handling and showing an H-value intermediate between those of potassium *tert*-butoxide and dimethylpotassium in DMSO (86IZV751). A mathematical model for evaluating the H-value of the superbase MOH/DMSO system has been suggested (87IZV1785) which takes into consideration the equilibrium, hydration and ion association in solution and fits the experimental data.

#### D. EFFECT OF THE ACETYLENE PRESSURE AND ENGINEERING OF THE REACTION

In an autoclave, the heterocyclization of ketoximes with acetylene into pyrroles and *N*-vinylpyrroles is normally performed under an initial pressure of 8–16 atm (commonly 10–12 atm). A maximal pressure developed in the reaction can amount to 30–35 atm. According to labor laws adopted in the USSR and most other countries, in industry it is forbidden to run processes based on acetylene under an excess pressure higher than 1.5 atm (with the exception of compressed and dissolved acetylene in cylinders intended for welding and metal cutting). Therefore, pressure becomes a key parameter as far as engineering aspects of such reactions are concerned.

These limitations were imposed after experiments dealing with the explosive properties of acetylene, which led to tragic outcomes at the dawn of the acetylene industry (cf. 69MI1 and references therein). The acetylene processing under pressure initiated by Reppe (56LA128; 60MI1; 66MI1) was developed against the existing safety regulations. However, its use in manufacturing plants for a long time has shown it to be safe. In order to minimize explosion properties, acetylene was diluted (phlegmatized) with inert gases, normally with nitrogen or saturated hydrocarbons (68MI2). In Germany during World War II there were two commercial plants each with an output of 5,000 tons per year. The production of methyl vinyl ether operated under an acetylene pressure at as much as 22 atm (49MI1). In the Soviet Union, on the basis of investigations carried out by Favorsky and Shostakovsky and independently by Reppe, a more extensive technology for vinylation of lower alcohols with compressed nondiluted acetylene has been developed, since the vapors of these alcohols and their vinyl ethers themselves were shown to be safe phlegmatizers in the gas phase (52MI1).

Analysis of the experimental data accumulated indicates the rate of formation of pyrroles, which can roughly be estimated by the amount of products formed for the standard time, is approximately in a direct relationship to the acetylene pressure. Since this relationship is typical for many processes of the "liquid-gas" type, the questions of how fast the synthesis of pyrroles proceeds under an excess pressure of about 1.5 atm and whether this is acceptable from the viewpoint of technology are of utmost importance.

Experiments on the synthesis of 4,5,6,7-tetrahydroindole and 1-vinyl-4,5,6,7-tetrahydroindole from cyclohexanone oxime and acetylene on bench reactors of 5 and 25 L performed under a 1.5 atm pressure give positive answers to these questions. Thus, at 100°C and KOH concentration of 0.4 mol/L, the output of 1 L of catalyst solution can amount to 50–100 g of pyrroles per hour. This means that in a small 1 m<sup>3</sup> reactor, it is possible to produce up to 400 tons of 4,5,6,7-tetrahydroindoles (1 and/or 2) per year, which is quite acceptable to meet an initial demand for these products. It can initiate, for instance, a cheap indole manufacture by catalytic dehydrogenation of tetrahydroindoles 1 and 2.

These results provided evidence of a high commercial feasibility of this reaction and laid the basis for development of a new process for manufacturing various pyrroles and their *N*-vinyl derivatives tested on a bench-plant (Fig. 5) (84M11): an enameled 60 L reactor (1) equipped with a turbine-type stirrer (320 rev/min), a jacket for vapor or cold water feeding, a rotameter (9) for controlling the acetylene feed rate and an explosive valve (8) for pressure release from the reactor, a 20 L extractor (2) with a stirrer (32 rev/min), a 30 L enameled distillator (3) with a glass refluxer column (10) and glass cooler (11), a 20 L glass collector of distillate (4), steel traps (5,7) and a vacuum pump (6).

Operation of the plant on a large scale has shown that when the reaction is carried out in DMSO using KOH in an amount of 1 mol per 1 mol of cyclohexanone oxime, it is possible to obtain 1-vinyl-4,5,6,7-tetrahydroindole in a yield higher than 80% and purity of up to 99% under an acetylene pressure from 0.3 to 1.5 atm without heat supply, at the expense of the exothermic character of the process.

Further investigations were completed by the development of conditions under which the synthesis of pyrroles and their *N*-vinyl derivatives can be performed under atmospheric pressure in a simple apparatus equipped with a stirrer and a bubbler for acetylene supply (reaction temperature 93–97°C). For this purpose, the alkali concentration must be increased in the reaction mixture to 50% of the ketoxime mass; the reaction must also be run approximately twice as long. In most cases the yield of pyrroles remains high:  $\geq 80\%$  (cf. Sections III.A–D).

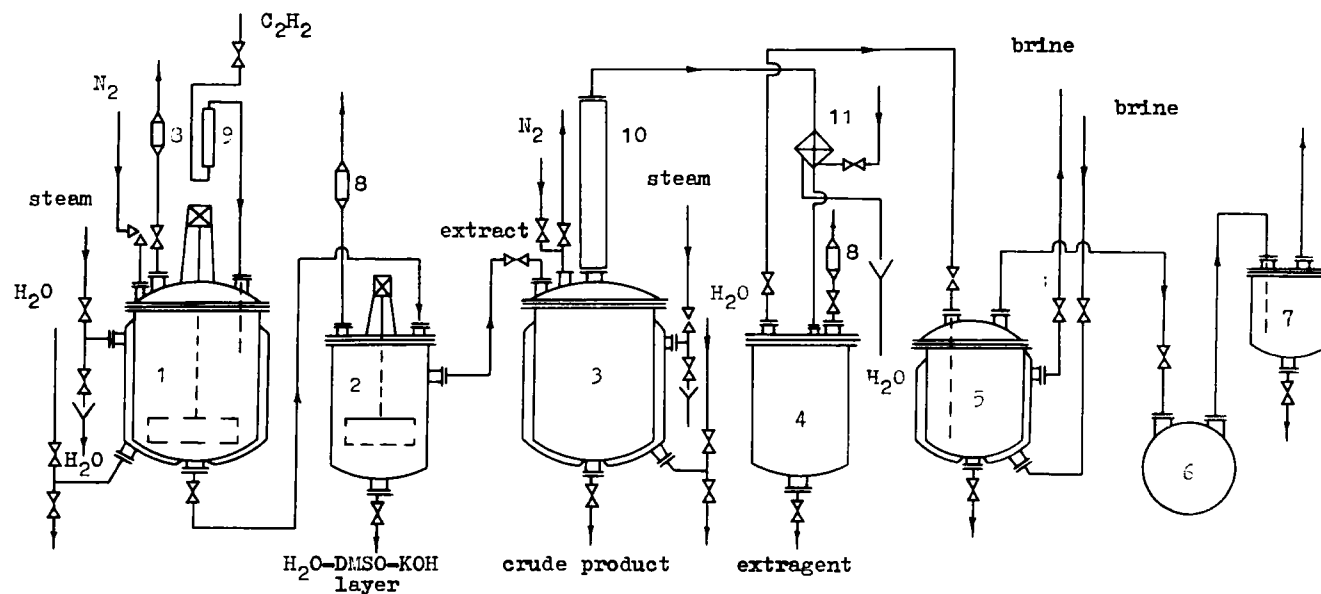


FIG. 5. Bench-scale production of pyrroles from ketoximes and acetylene (84MI1): 1, reactor; 2, extractor; 3, stripper; 4, extragent collector; 5, extragent trap; 6, vacuum pump; 7, extragent trap; 8, explosive valve; 9, rotameter; 10, refluxer column; 11, cooler.

### III. Influence of the Ketoxime Structure on the Yield and Ratio of Pyrroles

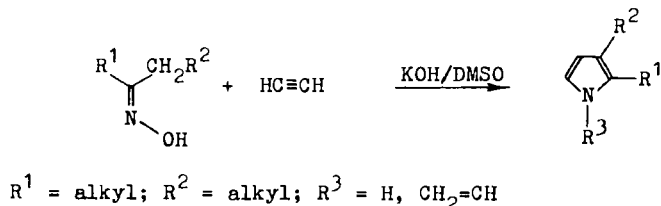
The reaction of heterocyclization with acetylene to form *NH*- and *N*-vinylpyrroles involves all ketones having at least one methylene or methyl group in the  $\alpha$ -position to the oxime function and no substituents susceptible to the action of bases (80KGS1299; 81MI4; 84MI1).

#### A. SYMMETRIC DIALKYL KETOXIMES

When acetylene reacts with symmetric ketoximes (75MIP1; 79MIP1, 79ZOR602), the corresponding 2-alkyl- and 2,3-dialkylpyrroles and their *N*-vinyl derivatives are formed (Scheme 3). The yields and physicochemical constants of some typical representatives of the pyrroles synthesized are given in Table VIII.

The high yields of pyrroles and their *N*-vinyl derivatives are achieved not only when the reaction is carried out in an autoclave under an acetylene pressure of 10–20 atm (75MIP1), but also, as stated previously, in the simplest apparatus equipped with a stirrer (with a continuous acetylene feed) under only slightly elevated (1.5 atm) or atmospheric pressure (79MIP1). The synthesis of pyrroles in an autoclave was performed at 120–140°C. With a large excess of acetylene and KOH in amounts of 1–30% of the ketoxime mass and a DMSO/ketoxime volume ratio within 1 : 8–1 : 16, the reaction is over in 1–3 hr. The yield of pyrroles is 72–95%. If the alkali content is increased to 1–2 mol per 1 mol of ketoxime, the reaction proceeds much faster: even under atmospheric pressure and lower temperature (93–97°C), it takes only about 3 hr for the reaction to be over, the yield remaining high (80%).



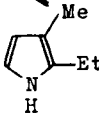
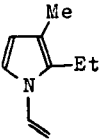
A process for the selective preparation of *NH*-pyrrole from oximes of aliphatic and alicyclic ketones and acetylene in an autoclave under pressure (yield 70–80%) with DMSO containing up to 10% of water as a solvent (120–140°C, 1–2 hr, 10% KOH) has been developed (76MIP1). According to Mikhaleva and co-workers (79ZOR602), the pyrroles were obtained

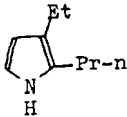
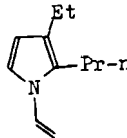
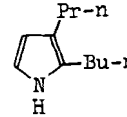
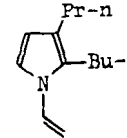


SCHEME 3



TABLE VIII  
REPRESENTATIVES OF PYRROLES PREPARED FROM DIALKYL KETOXIMES

Pyrrole	Structural formula	Yield (%)	b.p., °C (mm Hg)	d <sub>4</sub> <sup>20</sup>	n <sub>D</sub> <sup>20</sup>	Reference
2-Methylpyrrole		42	75 (50)	0.9426	1.5010	(79ZOR602)
2-Methyl-1-vinylpyrrole		54	39-40 (10)	0.9308	1.5230	(79ZOR602)
2-Ethyl-3-methylpyrrole		72 90	60.5 (4)	0.9206	1.5070	(79ZOR602) (82MIP1)
2-Ethyl-3-methyl-1-vinyl-pyrrole		57 70	59-60 (6)	0.9158	1.5175	(75MIP1) (79ZOR602)

3-Ethyl-2-n-propylpyrrol		73 83	84.5 (3)	0.8365	1.4950	(79ZOR602) (82MIP1)
3-Ethyl-2-n-propyl-1-vinylpyrrole		73	86-87 (3)	0.9020	1.5160	(79ZOR602)
2-n-Butyl-3-n-propyl-pyrrol		72 72	90-91 (1)	0.8800	1.4860	(79ZOR602) (79MIP1)
2-n-Butyl-3-n-propyl-1-vinylpyrrole		95 85	86-87 (2)	0.8925	1.5025	(79ZOR602) (75MIP1)

---

from oximes of aliphatic ketones and acetylene in a yield of up to 73% in a flask with acetylene bubbling (atmospheric pressure, 93–100°C, 6–10 hr, 40–100% KOH) in DMSO containing from 4 to 10% of water, which suppressed the reaction of vinylation to a larger extent than that of pyrrole formation.

The reaction of acetoxime with acetylene under the conditions optimal for the synthesis of pyrroles from other ketoximes affords lower yields of 2-methyl- and 2-methyl-1-vinylpyrrole, only 42% (40% KOH, 1 : 10 acetoxime/DMSO ratio, 4% water of DMSO volume, 97–100°C, 14–18 hr). Under analogous conditions, other ketoximes are converted to pyrroles in a yield of about 70%. Under the best conditions for the synthesis of *N*-vinylpyrroles, 2-methyl-1-vinylpyrrole is obtained in yields of 7–21%. In order to find the reason for such a low conversion of acetoxime to the *N*-vinylpyrrole, the authors varied the reaction conditions: thus the synthesis was performed in an autoclave under an acetylene pressure of 10–20 atm, in a bench reactor (acetylene pressure of about 1.5–2.0 atm), and under atmospheric pressure with the KOH and DMSO concentration temperature and reaction time being varied in a wide range (Table IX).

Table IX shows that at 130°C in an autoclave (12 atm acetylene pressure, 30% KOH, oxime/DMSO ratio 1 : 15), the synthesis is completed in 3 hr, the yield of 2-methyl-1-vinylpyrrole being increased up to 45% (run 4). The highest yield of 2-methyl-1-vinylpyrrole (54%) was achieved under atmospheric pressure (oxime/DMSO 1 : 10, 120–140°C, 21 hr) and with addition of 40% KOH in portions every 5–6 hr (run 6). If the KOH concentration is

TABLE IX  
TYPICAL EFFECTS OF REACTION CONDITIONS ON THE YIELD OF 2-METHYL-1-VINYLPYRROL IN THE REACTION OF ACETOXIME WITH ACETYLENE<sup>a</sup>

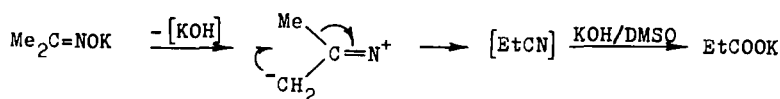
Run	Conc. of KOH (%) <sup>b</sup>	Volume ratio Acetoxime : DMSO	Temp. (°C)	Time (hr)	Yield (%)
1	10	1 : 8	140	1	21
2	30	1 : 5	120	3	17
3	30	1 : 24	120	1	40
4	30	1 : 15	130	3	45
5 <sup>c</sup>	30	1 : 5	110	16–18	40
6 <sup>d</sup>	40	1 : 10	120–140	21	54
7 <sup>d</sup>	50	1 : 10	120–140	15–18	50
8	50	1 : 10	120–140	4	24
9	100	1 : 10	97	14	7

<sup>a</sup> Runs 1–4 were performed in an autoclave (initial acetylene pressure 12 atm), runs 6–9 in a flask at 1 atm. From reference (79ZOR602).

<sup>b</sup> Of acetoxime mass.

<sup>c</sup> In a 5 L bench reactor (acetylene pressure 1.5–2.0 atm).

<sup>d</sup> KOH was added to the reaction mixture in portions every 5–6 hr.

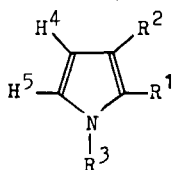


SCHEME 4

increased to 50%, and KOH is added not batchwise but all at once, and other conditions being equal (run 8), all the oxime is consumed in 4 hr, the yield of 2-methyl-1-vinylpyrrole dropping to 24%. Further increase in the KOH concentration to 100% (97°C, 14 hr) reduces the yield of 2-methyl-1-vinylpyrrole to 7% (run 9). Analysis of the reaction mixture and products by means of gas-liquid chromatography (GLC),  $^1\text{H}$  NMR, and IR spectroscopy has shown the acetoxime under these conditions to be completely spent in the reaction. However, no distillable byproducts (such as 1-butyne-3-ol, *O*-vinylacetoxime, or pyridine) were found. Possibly under these conditions the acetoxime is partially converted to the propionic acid salt (Scheme 4). Unfortunately, this was not checked in the work by Mikhaleva *et al.* (79ZOR602): salt composition of the reaction mixture has not been examined.

A considerable amount of nondistillable resinous residue always found in the distillation of crude product suggests (79ZOR602) that 2-methyl-1-vinylpyrrole is more readily polymerized than other *N*-vinylpyrroles under

TABLE X  
COMPARISON OF TYPICAL CHEMICAL SHIFTS OF PROTON SIGNALS (PPM) OF *NH*- AND *N*-VINYLPIRROLES (79ZOR602)



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	H <sup>3</sup>	H <sup>4</sup>	H <sup>5</sup>	H <sup>A</sup>	H <sup>B</sup>	H <sup>C</sup>
Me	H	H	5.75	5.92	6.31			
Me	H	CH <sub>2</sub> =CH <sup>a</sup>	5.74	5.99	6.72	4.93	4.47	6.72
Et	Me	H		5.76	6.23			
Et	Me	CH <sub>2</sub> =CH <sup>a</sup>		5.91	6.69	4.81	4.35	6.66
<i>n</i> -Pr	Et	H		5.80	6.32			
<i>n</i> -Pr	Et	CH <sub>2</sub> =CH <sup>a</sup>		5.95	6.79	4.90	4.43	6.73
<i>n</i> -Bu	<i>n</i> -Pr	H		5.80	6.32			
<i>n</i> -Bu	<i>n</i> -Pr	CH <sub>2</sub> =CH <sup>a</sup>		5.96	6.75	4.85	4.40	6.75

<sup>a</sup> Protons of the vinyl group are designated as follows

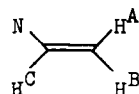


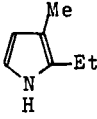
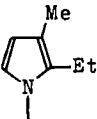
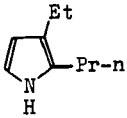
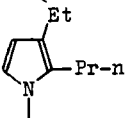
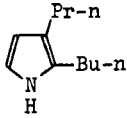
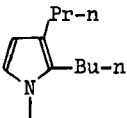


TABLE XI  
COMPARISON OF UV SPECTRA OF *NH*- AND *N*-  
VINYLPIRROLES (CYCLOHEXANE)<sup>a</sup>

Pyrrole	$\lambda_{\max}$ , nm (log $\epsilon$ )	Pyrrole	$\lambda_{\max}$ , nm (log $\epsilon$ )
	217 (3.86)		202 (4.00) 248 (4.10)
	213 (3.94)		202 (4.08) 254 (4.10)
	222 (3.89)		201 (4.05) 254 (4.07)
	222 (3.90)		201 (4.08) 254 (4.08)


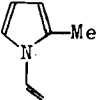
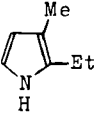
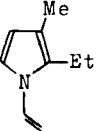
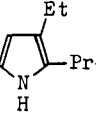
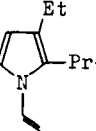
<sup>a</sup> From reference (79ZOR602).

the reaction conditions, which may be one of the reasons for the decrease in the yield. This is in agreement with other information concerning *N*-vinylpyrrole polymerization (87MI1). It is quite possible, however, that a high yield of 2-methylpyrrole and its *N*-vinyl derivative cannot be achieved because of participation of acetoxime in autocondensation processes similar to those leading to pyridines in an aqueous medium (cf. Sections II.C.2 and IV.F).

The structure and individuality of the *NH*- and *N*-vinylpyrroles synthesized are confirmed by GLC, <sup>1</sup>H NMR, IR, and UV spectroscopy. Their typical <sup>1</sup>H-NMR spectra (Table X) show characteristic doublets of ring H<sup>4</sup> and H<sup>5</sup> protons at 5.76–5.99 and 6.23–6.79 ppm, respectively. The *N*-vinyl group is displayed as a weak CH proton quartet in the 6.66–6.75 ppm region, overlapped with the H<sup>5</sup> and H<sup>A</sup> and H<sup>B</sup> doublets (4.81–4.93 and 4.35–4.47 ppm, respectively) in some cases (75KGS360).

The typical UV spectra (Table XI) of pyrroles unsubstituted at the nitrogen atom contain (74MI4) one absorption maximum 217–222 nm,

TABLE XII  
COMPARISON OF TYPICAL IR SPECTRA OF *NH*- AND *N*-VINYLPIRROLES<sup>a</sup>

Pyrrole	$\nu$ , $\text{cm}^{-1}$
	570, 650, 705, 783, 882, 953, 973, 1030, 1080, 1120, 1200, 1275, 1320, 1380, 1425, 1462, 1545, 1572, 2860, 2915, 2980, 3100, 3130
	597, 615, 705, 780, 870, 975, 980, 1030, 1050, 1085, 1120, 1160, 1220, 1250, 1290, 1320, 1365, 1420, 1485, 1540, 1570, 1632, 2870
	550, 642, 700, 720, 785, 885, 900, 968, 1020, 1062, 1108, 1226, 1252, 1290, 1320, 1393, 1463, 1544, 1580, 2880, 2930, 2970, 3110, 3130, 3390
	580, 620, 705, 780, 857, 960, 985, 1055, 1115, 1168, 1234, 1250, 1330, 1390, 1435, 1490, 1540, 1587, 1640, 2850, 2935, 2960, 3110,
	555, 650, 700, 720, 785, 835, 900, 957, 1010, 1050, 1090, 1106, 1202, 1240, 1270, 1333, 1373, 1463, 1543, 1573, 2880, 2940, 2970, 3100, 3390
	580, 700, 860, 940, 960, 1060, 1120, 1160, 1220, 1250, 1310, 1380, 1420, 1465, 1490, 1544, 1582, 1642, 2880, 2940, 2970, 3110

<sup>a</sup> From reference (79ZOR602).

whereas their *N*-vinylpyrrole derivatives absorb in two regions, 201–202 and 248–254 nm (75KGS1225).

In the typical IR spectra of the pyrroles (Table XII), there are characteristic bands corresponding to the pyrrole ring: 700–712  $\text{cm}^{-1}$  (C—H pyrrole ring deformations), 1365–1390, 1462–1490, 1538–1587  $\text{cm}^{-1}$  (pyrrole framework vibrations) and to the *N*-vinyl group: 580–597, 940–988  $\text{cm}^{-1}$  ( $\text{CH}_2=$  and  $\text{HC=CH}$  deformations), 1632–1643  $\text{cm}^{-1}$  (C=C stretching) (77KGS910).

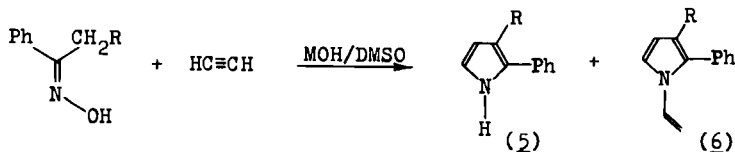
## B. ALKYL ARYL KETOXIMES

Oximes of alkyl phenyl ketones were successfully involved in the reaction with acetylene (Scheme 5). In this way, previously unavailable 3-alkyl(phenyl)-2-phenylpyrroles (**5**) and previously unknown 3-alkyl(phenyl)-2-phenyl-1-vinylpyrroles (**6**) (Table XIII) were prepared (78ZOR-2182).

In this case the reaction proceeds readily upon heating (100°C, 3 hr) alkyl phenyl ketoximes with acetylene under pressure (initial pressure 10–14 atm) in DMSO in the presence of 20–30% (of ketoxime mass) of lithium hydroxide (when *NH*-pyrroles **5** are to be prepared) or potassium hydroxide (when the synthesis of *N*-vinylpyrroles **6** is the target). With less acetylene, the corresponding 3-alkyl(phenyl)-2-phenylpyrrole (**5**) is the major reaction product. The highest yields of *NH*-pyrroles (**5**), however, were achieved when LiOH was employed (78MIP2, 78ZOR2182). As mentioned previously (Section II.C.1), this catalyst, while effectively accelerating pyrrole ring construction, is practically inactive at the vinylation stage. In some cases (especially with LiOH), the synthesis of *N*-unsubstituted pyrroles (**5**) is accompanied by partial regeneration of alkyl phenyl ketones. With excess acetylene the reaction occurs further with the formation of 3-alkyl(phenyl)-2-phenyl-1-vinylpyrroles (**6**).

Under these relatively harsh conditions, the structure of the initial alkyl phenyl ketoximes does not much affect the yield of *N*-vinylpyrroles (**6**), although a tendency towards some gains in yield with increasing number of carbon atoms in the alkyl radical is noted (Table XIII).

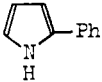
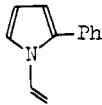
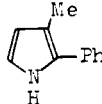
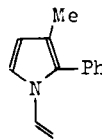
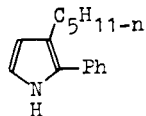
It was intended (85KGS1501) to find milder synthetic conditions for further simplifying the purification of 3-alkyl-2-phenylpyrroles (**5,6**) (Scheme 5). It was necessary to increase the DMSO content of the reaction mixture. So, when the synthesis was carried out under pressure in a 10-fold excess (of the total mass of reagents) of DMSO with an equimolar (with respect to ketoxime) amount of KOH, it was possible to decrease considerably the reaction temperature (to 50–60°) and prepare 3-alkyl-2-arylpyrroles (**5**) and their 1-vinyl derivatives (**6**) (which more readily undergo purification) in total yield up to 90%.



M = Li, K; R = H, Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *n*-C<sub>5</sub>H<sub>11</sub>, *n*-C<sub>6</sub>H<sub>13</sub>,  
*n*-C<sub>7</sub>H<sub>15</sub>, *n*-C<sub>8</sub>H<sub>17</sub>, *n*-C<sub>9</sub>H<sub>19</sub>, Ph

SCHEME 5

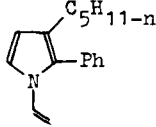
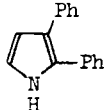
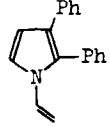
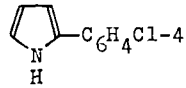
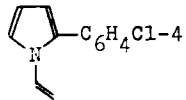
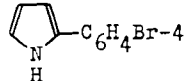
TABLE XIII  
REPRESENTATIVES OF ARYLPYRROLES PREPARED FROM ALKYL ARYL KETOXIMES

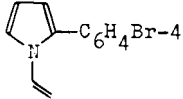
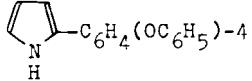
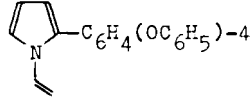
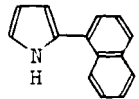
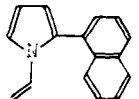
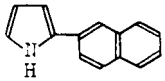
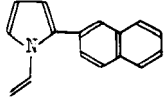
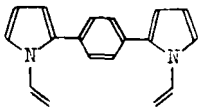
Pyrrole	Structural formula	Yield (%)	b.p., °C (mm Hg) m.p., °C	$d_4^{20}$	$n_D^{20}$	Reference
2-Phenylpyrrole		64 73	m.p., 129			(78ZOR1733) (78MIP2) (79MIP1)
2-Phenyl-1-vinyl-pyrrol		70	b.p., 94 (1)	1.0443	1.6190	(78ZOR1733) (78KGS489) (78ZOR2182)
3-Methyl-2-phenyl-pyrrol		38	m.p., 34			(78ZOR1733) (78ZOR2182)
3-Methyl-2-phenyl-1-vinyl		76 29-38	b.p., 110 (1-2)	1.0509	1.5960	(78ZOR1733) (78ZOR2182)
3- <i>n</i> -Amyl-2-phenyl-pyrrol		58	b.p., 146 (1)	1.005	1.5751	(78ZOR2182)

(continued)



TABLE XIII (Continued)

Pyrrole	Structural formula	Yield (%)	b.p., °C (mm Hg) m.p., °C	d <sub>4</sub> <sup>20</sup>	n <sub>D</sub> <sup>20</sup>	Reference
3- <i>n</i> -Amyl-2-phenyl-1-vinylpyrrole		79	b.p., 145 (1-2)	0.9764	1.5670	(78ZOR2182)
2,3-Diphenylpyrrole		72	m.p., 127			(78ZOR2182) (78MIP2)
2,3-Diphenyl-1-vinyl-pyrrole		73	m.p., 109-110			(78ZOR2182)
2-(4-Chlorophenyl)-pyrrole		65 71	m.p., 140 m.p., 140			(78KGS489) (84ZOR1960)
2-(4-Chlorophenyl)-1-vinylpyrrol		65	b.p., 120 (1)	1.1674	1.6290	(78KGS489)
2-(4-Bromophenyl)-pyrrole		36	m.p., 158-160			(84ZOR1960)

2-(4-Bromophenyl)-1-vinylpyrrole		22	b.p., 123–124 (1)	1.3860	1.6469	(78KGS489)
2-(4-Phenoxyphenyl)-pyrrole		43	m.p., 152–154			(78KGS489)
2-(4-Phenoxyphenyl)-1-vinylpyrrole		55	b.p., 188–190 (1)	1.0953	1.6150	(78KGS489)
2-(1-Naphthyl)-pyrrole		22	m.p., 179–180			(82KGS1351)
2-(1-Naphthyl)-1-vinyl-pyrrole		49	m.p., 48–50			(82KGS1351)
2-(2-Naphthyl)pyrrole		64	m.p., 154–155			(82KGS1351)
2-(2-Naphthyl)-1-vinyl-pyrrole		62	m.p., 50–51			(82KGS1351)
1,4-Bis(1-vinyl-2-pyrrolyl)benzene		30	m.p., 130–133			(82ZOR2620)

In this case, the composition of the net product and the yield of pyrroles are considerably affected by the structure of the ketoxime (Table XIV). Thus, under these conditions 2-phenylpyrrole (from methyl phenyl ketoxime) was formed in a yield of only about 10%, whereas under the same conditions, 3-*n*-amyl-2-phenylpyrrole (from *n*-hexyl phenyl ketoxime) was isolated in 83% yield along with the corresponding *N*-vinylpyrrole (6%). In general, with lengthening of the alkyl radical chain from Me to *n*-C<sub>10</sub>H<sub>21</sub>, the total yield of pyrroles at first increased (to R = C<sub>5</sub>—C<sub>6</sub>) and then begins to drop, although it still remains fairly high (50–72%). The extreme character of the yield/R relationship (Table XIV) seems to be related to not only electronic effects of substituents, but to a change in the hydrophobic–hydrophilic balance in molecules of the initial and final substances, i.e., to the degree of their solubility in the reaction mixture. A tendency to weakening the capability of oximes for heterocyclization when the electronegativity of the R radical increases is noticeable. Methyl phenyl ketoxime, for example, is more inclined towards the formation of its *O*-vinylation product (22%) which, under the conditions studied (50°C, 3 hr), is not completely transformed into pyrrole (see Sections IV.A and V.A). Interestingly, a similar result was obtained with methyl 4-chlorophenyl ketoxime. The electron-donating properties of its anion weakened compared with the anions of alkyl phenyl ketoximes, due to the chlorine atom. Under the same conditions, the yield of pyrrole from this oxime is 8%, whereas that of the intermediate *O*-vinylloxime is 17% (85KGS1501).

3-Alkyl-2-phenylpyrrole are readily formed, according to Scheme 5, under atmospheric pressure as well (50–70°C, 5–10 hr, equimolar amount or slight excess of KOH relative to oxime, excess of DMSO). Table XV illustrates the effects of the reaction temperature and time as well as of the structure of ketoximes on the composition and the yield of end products.

The pyrroles synthesized have typical IR, <sup>1</sup>H, <sup>13</sup>C NMR, and UV spectra. The IR spectrum of 2-phenylpyrrole, for example, shows the following absorption bands (cm<sup>−1</sup>): 3400, 3438 (N—H), 698, 1500, 1607 (pyrrole and phenyl moieties) (77KGS910). The <sup>1</sup>H-NMR spectrum of this pyrrole (ppm) has 8.03 (broadened NH signal), 6.65 m, 6.35 m, 5.92 m (pyrrole ring, 3 Hz), 7.27 (phenyl); <sup>13</sup>C NMR of the pyrrole ring (ppm) shows 132.12 (C<sup>2</sup>), 106.08 (C<sup>3</sup>), 106.08 (C<sup>4</sup>), 119.84 (C<sup>5</sup>).

The IR spectrum of 2-phenyl-1-vinylpyrrole (cm<sup>−1</sup>) includes bands 586, 872, 976, 1582, 1642 (NCH=CH<sub>2</sub>) (77KGS910), 704, 1360 (pyrrole ring), 1323 (C—N for *N*-substituted pyrroles), 1500 and 1602 (phenyl and pyrrole moieties). In the <sup>1</sup>H-NMR spectrum of this pyrrole, the vinyl protons (see Table X for designation) are represented by signals (ppm) 4.98 d (H<sup>A</sup>), 4.49 d (H<sup>B</sup>), 6.79 q (H<sup>C</sup>); pyrrole ring protons: 6.10 d (H<sup>3</sup>, H<sup>4</sup>), 6.95 t (H<sup>5</sup>); phenyl protons: 7.2 m. The UV spectrum [cyclohexane, λ<sub>max</sub>, nm (log ε)] displays absorption: 208 (4.11), 270 (4.12), 250 (4.10).

TABLE XIV  
EFFECT OF ALKYL STRUCTURE ON THE CONVERSION OF ALKYL  
PHENYL KETOXIME<sup>a</sup> AND THE YIELD OF  
3-ALKYL-2-PHENYLPYRROLES (5,6)<sup>b</sup>

R	Conversion of oxime (%)	Yield (%)	
		NH-Pyrrole 5	N-Vinylpyrrole 6
H	35	10	trace amounts
Me	52	36	trace amounts
Et	40	38	trace amounts
<i>n</i> -Pr	90	47	13
<i>i</i> -Pr	71	26 ± 2 <sup>c</sup>	4
<i>n</i> -Bu	100	63	20
<i>n</i> -C <sub>5</sub> H <sub>11</sub>	92	83	6
<i>n</i> -C <sub>6</sub> H <sub>13</sub>	61	44 ± 3 <sup>c</sup>	8
<i>n</i> -C <sub>7</sub> H <sub>15</sub>	89	48	9
<i>n</i> -C <sub>8</sub> H <sub>17</sub>	92	49	17
<i>n</i> -C <sub>9</sub> H <sub>19</sub>	92	57	13

<sup>a</sup> 50–60°C, KOH equimolar amount with respect to ketoxime, ten-fold excess of DMSO (of total mass of reagents), initial C<sub>2</sub>H<sub>2</sub> pressure 12–14 atm.

<sup>b</sup> From reference (85KGS1501), see also Scheme 5.

<sup>c</sup> From data of two runs.

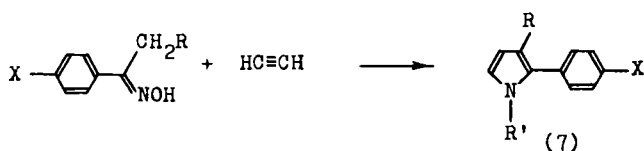
TABLE XV  
EFFECT OF CONDITIONS ON THE CONVERSION OF KETOXIMES AND THE YIELD OF PYRROLES<sup>a</sup>

R	Temp. (°C)	Time (hr)	Conversion of oxime (%)	Yield (%)	
				NH-Pyrrole 5	N-Vinylpyrrole 6
H <sup>b</sup>	40	10	15	trace amounts	not detected
H	60	2.5	22	trace amounts	not detected
H <sup>b</sup>	60	10	55		not detected
Et	70	5	51	36	9
<i>n</i> -Pr	50	5	21	11	0.3
<i>n</i> -Pr	70	5	49	33	1
<i>i</i> -Pr	70	5	76	54	6

<sup>a</sup> Reaction done under atmospheric pressure. From reference (85KGS1501). See also Scheme 5.

<sup>b</sup> Twofold mol excess of KOH was used.

The pyrrolization of various alkyl aryl ketoximes (Scheme 6) was also studied [78KGS489; 84ZOR1960; 90ZOR(ip)], and it was confirmed that the corresponding 2-arylpyrroles (7) could also be obtained successfully in this way (see Table XIII).



X = H, Me, Et, i-Pr, t-Bu, F, Cl, Br, MeO, PhO, EtS, PhS;

R = H, alkyl; R' = H,  $\text{CH}_2=\text{CH}$

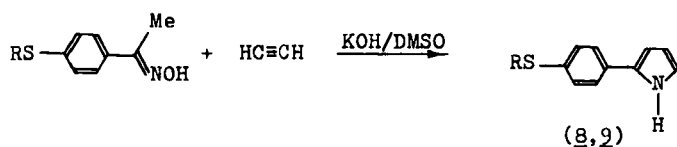
SCHEME 6

The reaction proceeds smoothly at 80–100°C in the presence of 30% (of the ketoxime mass) KOH in DMSO in an autoclave under an initial acetylene pressure of 8–16 atm. The highest pressure developed when the reaction mixture reached a prescribed temperature, is 20–25 atm. Then fast absorption of acetylene starts and the pressure reduces rapidly. For preparing *N*-vinylpyrroles at least a twofold excess of acetylene is employed. If the corresponding *NH*-pyrrole is to be obtained the synthesis is performed with the calculated or a deficient amount of acetylene. Here again, lithium hydroxide is a selective catalyst for pyrrole ring formation. When LiOH is used, no precise batching of acetylene is required.

As seen in Table XIII, the yield of 2-aryl-1-vinylpyrroles depends much on the benzene ring substituent. The sharp decrease in the yield of 4-bromophenyl-1-vinylpyrrole (from 4-bromoacetophenone oxime) is expected: it is caused by reaction at the bromine atom with the strong base. No success was attained in an attempt to obtain pyrrole from 4-nitroacetophenone oxime under the conditions studied as a result of instability of the substituent in the super base medium.

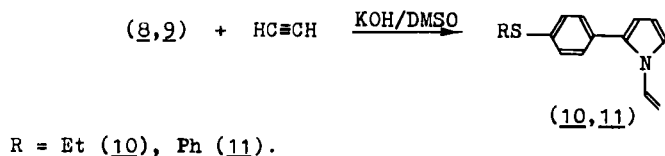
Due to the isolation from natural sources of new antibiotics relating to the arylpyrroles, the interest in this class of compounds has grown greatly (74MI1; 77MI1; 81MI2, 81MI3).

Unknown until recently, 2-(4-ethylthio)- and 2-(4-phenylthiophenyl)-pyrroles (**8,9**) are formed in a yield of up to 48% by the reaction of 4-ethylthio- and 4-phenylthio-acetophenone oximes with acetylene under atmospheric pressure at 96°C (Scheme 7) [90ZOR(ip)].



R = Et (**8**), Ph (**9**).

SCHEME 7



SCHEME 8

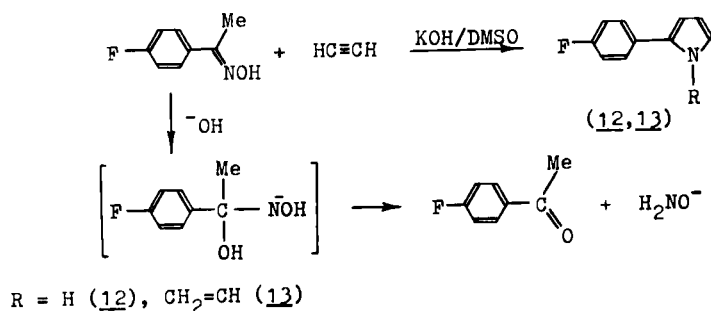
The moderate yield of pyrroles **8** and **9** seems to be related to cleavage of the C—S bond (81MI4). Vinyl derivatives **10** and **11** were prepared by direct vinylation of pyrroles **8** and **9** by acetylene under atmospheric pressure (120°C, 5 hr, pyrrole/KOH molar ratio 1 : 5) (Scheme 8) [90ZOR(ip)]. 2-(4-Ethylthiophenyl)-1-vinylpyrrole (**10**) was isolated in 48% yield.

During condensation of 4-fluoroacetophene oxime with acetylene, along with possible substitution of fluorine, the regeneration of 4-fluoroacetophenone (yield 24%) becomes a prominent process, as compared with other oximes, especially when calcined potassium hydroxide and dry DMSO are used (Scheme 9). Ketone is likely to form owing to nucleophilic addition of the hydroxide anion to the C=N bond of oxime [90ZOR(ip)].

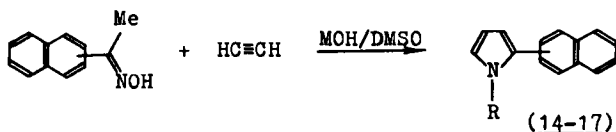
2-(4-Fluorophenyl)pyrrole (**12**) was prepared in 11% yield when the reaction was carried out in an autoclave (90°C, initial pressure 12 atm). 2-(4-Fluorophenyl)-1-vinylpyrrole (**13**) is formed under these conditions as an impurity. However, pyrrole **13** was also obtained by direct vinylation of the pyrrole **12** with acetylene under atmospheric pressure (125–135°C, pyrrole/KOH molar ratio 1 : 1.5) in 70% yield [90ZOR(ip)].

The condensation of methyl perfluorophenyl ketone oxime with acetylene (KOH/DMSO, 100°C, 2 hr, 12 atm) failed to afford the expected pyrrole [90ZOR(ip)].

Information concerning naphthylpyrroles is scarce up to now (D4 CB2792; 59GEP1105713; 68FRP1549829; 75MI4; 79JOC494; 79CC363),



SCHEME 9



M = Li, K; 1-Naphthyl, R = H (14),  $\text{CH}_2=\text{CH}$  (15);

2-Naphthyl, R = H (16),  $\text{CH}_2=\text{CH}$  (17)

SCHEME 10

and their *N*-vinyl derivatives remained unknown until reported by Korotsova and co-workers (82KGS1351) in spite of their being of interest as monomers and starting material for the preparation of bioactive compounds.

It turned out that the acetylene-assisted pyrrolization of ketoximes could be successfully extended to oximes of condensed aromatic ketones, such as 1- and 2-acetylnaphthalenes (Scheme 10) (82KGS1351).

Under the conditions favorable for the synthesis of pyrroles from alkyl aryl ketoximes ( $100^\circ\text{C}$ , 3 hr, 30% KOH of ketoximes mass, DMSO, acetylene under 12–16 atm pressure), the reaction with methyl naphthyl ketoximes is accompanied by considerable resinification to give low yields of pyrroles 14–17. The best results were achieved at  $90^\circ\text{C}$ . From methyl 1-naphthyl ketoxime at this temperature (2 hr, KOH), 2-(1-naphthyl)pyrrole (14) and 2-(1-naphthyl)-1-vinylpyrrole (15) are formed in 15 and 48% yield, respectively.

In general, however, methyl 1-naphthyl ketoxime starts to condense with acetylene under pressure at about  $60^\circ\text{C}$ . At  $80^\circ\text{C}$  (3 hr, KOH) 2-(1-naphthyl)-1-vinylpyrrole (15) becomes the predominant reaction product, however its yield decreases due to resinification on further elevating the temperature and increasing the reaction time. 2-(1-Naphthyl)pyrrole (14), free from the corresponding *N*-vinylpyrrole (15), was isolated in 22% yield when use was made of a catalytic pair  $\text{LiOH/DMSO}$  ( $90^\circ\text{C}$ , 3 hr). The temperature effect (3 hr, 30% KOH, initial acetylenic pressure of 12 atm) on the yield of naphthylpyrroles was examined in condensation of methyl 2-naphthyl ketoxime with acetylene as an example (82KGS1351):

Reaction temp. ( $^\circ\text{C}$ )	Yield, %	
	2-(2-Naphthyl)- pyrrole (14)	2-(2-Naphthyl)-1- vinylpyrrole (15)
60	trace	not detected
70	33	trace
90	13	49
100	not detected	36

As in other cases, the nature of the alkali cation has a substantial effect on the yield and ratio of pyrroles **14–17**. If in the presence of KOH (70°C, 3 hr) the yield of 2-(2-naphthyl)pyrrole (**14**) is 33%, LiOH practically fails to catalyze the process at the same temperature.

Naphthylpyrroles (**14–17**) can be prepared in good yield under atmospheric pressure in a flask with a stirrer by passing acetylene through the heated (90–100°C) reaction mixture upon stirring. For 4–5 hr, the conversion of 2-methyl naphthyl ketoxime approaches 70%, the yield of 2-(2-naphthyl)pyrrole (**14**) being 64%. At 110–120°C (13 hr), the reaction goes further (although resinification also increases). As a result, the reaction mixture consists of 2-(2-naphthyl)pyrrole (**14**) and 2-(2-naphthyl)-1-vinylpyrrole (**15**) in a ratio of 1 : 2. From this mixture, it was possible to isolate pure products in 18 and 31% yields by chromatography on Al<sub>2</sub>O<sub>3</sub> (hexane/Et<sub>2</sub>O 3 : 1).

All the naphthylpyrroles (**14–17**) are crystalline substances (see Table XIII) soluble in diethyl ether, acetone, chloroform, DMSO, poorly soluble in ethanol, hexane, and insoluble in water. Typical <sup>1</sup>H-NMR spectra of these pyrroles are presented in Table XVI.

Until recently, there were no general approaches to the synthesis of arenes bearing several pyrrolic substituents, though these systems are rather interesting from theoretical and preparative viewpoints.

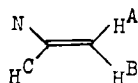
In the course of evaluating the area of application and limitation of pyrrole formation from ketoximes and acetylene, it has been found (82ZOR2620) that this may involve aromatic dioximes. From diacetylbenzene dioxime (**18**), for example, a one-stage transition to 1,4-bis(1-vinyl-2-pyrrolyl)benzene (**19**) was accomplished (Scheme 11).

TABLE XVI  
COMPARISON OF CHEMICAL SHIFTS OF PYRROLIC<sup>a</sup> AND VINYLIC<sup>b</sup> PROTONS OF 1- AND 2-NAPHTHYPYRROLES (**14,16**) AND THEIR VINYL DERIVATIVES (**15,17**) (82KGS1351)

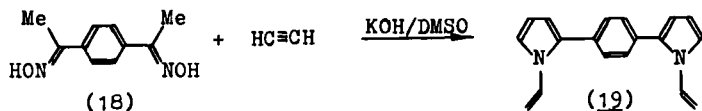
Pyrrole	Chemical shifts (ppm)					
	H <sup>3</sup>	H <sup>4</sup>	H <sup>5</sup>	H <sup>A</sup>	H <sup>B</sup>	H <sup>C</sup>
2-(1-Naphthyl)pyrrole ( <b>14</b> )	6.20	6.31	6.70			
2-(1-Naphthyl)-1-vinyl-pyrrole ( <b>15</b> )	6.17	6.25	7.07	4.96	4.33	6.40
2-(2-Naphthyl)pyrrole ( <b>16</b> )	6.17	6.44	6.72			
2-(2-Naphthyl)-1-vinyl-pyrrole ( <b>17</b> )	6.17	6.17	6.95	4.99	4.49	6.90

<sup>a</sup> Spin-spin coupling constants of the pyrrole ring protons in all compounds: <sup>3</sup>J<sub>34</sub>, 3.6; <sup>3</sup>J<sub>45</sub>, 3.2; <sup>4</sup>J<sub>35</sub>, 1.8 Hz.

<sup>b</sup> Vinyl group protons are designated as follows







SCHEME 11

The IR spectrum of 1,4-bis(1-vinyl-2-pyrrolyl)benzene (19) ( $\text{cm}^{-1}$ ) includes bands at 580, 600, 847, 960, 970, 1642 (vinyl group); 735, 1348, 1503, 1604 (pyrrole and benzene moieties). Its  $^1\text{H-NMR}$  spectrum (ppm) has signals at 5.03 d ( $\text{H}^{\text{A}}$ ), 4.58 d ( $\text{H}^{\text{B}}$ ), 6.85 q ( $\text{H}^{\text{C}}$ ), 6.08 d ( $\text{H}^3$ ,  $\text{H}^4$ ), 6.85 ( $\text{H}^5$ ), 7.27 m (Ph),  $J_{\text{AC}}$  15.5,  $J_{\text{BC}}$  8.25 Hz (for the vinylic protons see Table XVI).

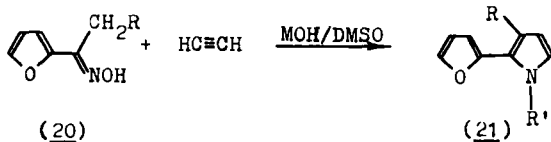
Thus, the reaction of diacetylarene dioximes with acetylene in the KOH/DMSO system provides a simple route to previously unknown bis-(pyrrolyl)arenes.

### C. ALKYL HETARYL KETOXIMES

The syntheses of hetarylpyrroles from ketoximes of the heteroaromatic series appeared in the late 1970s with the preparation of 2-(2-thienyl)pyrroles (77KGS1136) and 2-(2-furyl)-3-alkyl-1-vinylpyrroles (78ZOR2628). Some features of spin-spin coupling in their  $^1\text{H-NMR}$  spectra were reported (79IZV2372). This was a major and, to a certain extent, general solution of the problem of synthesizing compounds having the pyrrole ring linked with other heterocycles. As analogs of prodigiosins, compounds of this type are of interest as possible precursors of new chemotherapeutics [77M285; 85MI2; 86JCS(P1)455].

In spite of their being cited in a monograph (82AHC237), their publication (77KGS1136; 78ZOR2628; 79IZV2372) seems to have been missed by most specialists. So the search was focused on the development of more special and multistage methods (71ACS2596, 78AG719, 79TL-1717, 80CPB2384, 81KGS402, 82MIP2, 83KGS1062, 83KGS1067, 83-JAP5896063).

The experimental conditions for the reaction of alkyl furyl ketoximes (20) with acetylene (Scheme 12) were first described in detail by Trofimov and co-workers (81KGS1058). Under conditions close to those typical of



M = Li, K; R = H, Me, Et, n-Pr, i-Pr, n-Bu; R' = H,  $\text{CH}_2=\text{CH}$

SCHEME 12

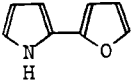
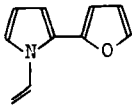
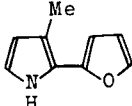
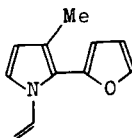
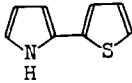
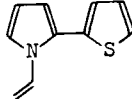
this reaction (100°C, oxime **20**/KOH molar ratio 5:3, excess acetylene under initial pressure of 14–15 atm), methyl furyl ketoxime with acetylene gives a 4:1 mixture of 2-(2-furyl)-1-vinylpyrrole (**21**, R = H, R' = CH<sub>2</sub>=CH) and its nonvinylated precursor (**21**, R = R' = H) in 71% yield (55 and 16%, respectively). From ethyl furyl ketoxime, under similar conditions, 2-(2-furyl)-3-methyl-1-vinylpyrrole (57%) and the corresponding *NH*-pyrrole (8%) are formed. At a higher temperature (130°C) and with an equimolar ratio of ethyl furyl ketoxime to KOH, only *N*-vinylpyrrole (**21**, R = Me, R' = CH<sub>2</sub>=CH) is obtained in 65% yield. Lithium hydroxide, which selectively catalyzed the pyrrole ring formation in an analogous reaction with alkyl aryl ketoximes (see Section III.B) as well as in reaction with phenyl benzyl ketoximes (78MIP2), does not show any selective effect in this case, e.g., from methyl furyl ketoxime even at 100°C, only a 3:2 mixture of furylpyrrole (**21**, R = R' = H) and its *N*-vinyl derivative are formed, the total yield of the pyrroles being much lower than that with KOH (35% instead of 72%). The best conditions for the synthesis of 2-(2-furyl)-1-vinyl pyrroles under acetylenic pressure are temperature, 110–130°C; excess acetylene; reaction time, 3 hr, oxime **20**/KOH molar ratio, 1:1. Under these conditions the yield of 2-(2-furyl)-1-vinylpyrroles ranges from 50 to 85% (see Table XVII). Below 100°C, the reaction rate is too low, whereas above 130°C, some side reactions involving both the initial substances (deoximation to ketones as evidenced from the absorption band at 1680 cm<sup>-1</sup> in the IR spectra of the reaction mixture) and final products (polymerization which seems to occur with participation of both the vinyl group and the ring) become prominent. At 130–140°C alkyl furyl ketoximes (**20**) readily form *N*-vinylpyrroles (**21**, R' = CH<sub>2</sub>=CH) at atmospheric pressure as well, although the reaction time increases up to 6–8 hr. At 100°C for 6 hr, ethyl furyl ketoxime and acetylene give a mixture of 2-(2-furyl)-3-methylpyrrole (18.5%) and 2-(2-furyl)-3-methyl-1-vinylpyrrole (33%) (81KGS1058).

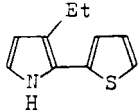
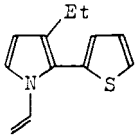
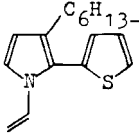
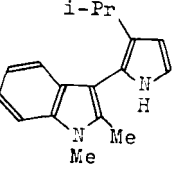
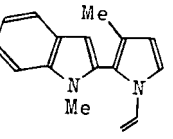
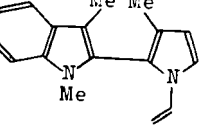
3-Alkyl-2-(2-furyl)-1-vinylpyrroles are high boiling liquids with a slight characteristic odor, soluble in diethyl ether, acetone, ethanole, chloroform, DMSO, and insoluble in water. Typical IR and UV spectra of these compounds are presented in Table XVIII. The <sup>1</sup>H-NMR spectra have been discussed in detail (78ZOR2628; 79IZV2372).

The <sup>1</sup>H-NMR spectrum of 2-(2-furyl)-3-methyl-1-vinylpyrrole is given here as typical (ppm): 2.0 (d, J 1.5 Hz, Me); 4.4, 4.5 (two doublets, J 8.0, 15.0 Hz, *N*-vinyl group β-protons); 6.0 (m, pyrrole H<sup>4</sup>); 6.0, 6.3 (m, furan H<sup>3</sup> and H<sup>4</sup>); 6.8 (d, J 2.0 Hz, pyrrole H<sup>5</sup>, overlapped with quartet of vinyl group α-proton) (78ZOR2628); 7.3 (d, furan H<sup>5</sup>) (81KGS1058).

Realization of this reaction with furyl ketoximes opens an easy access to a novel series of furylpyrroles having a reactive vinyl group ready for

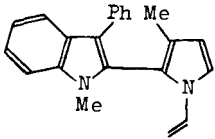
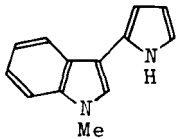
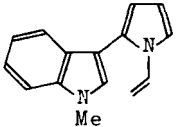
TABLE XVII  
REPRESENTATIVES OF HETARYLPYRROLES PREPARED FROM ALKYL HETARYL KETOXIMES

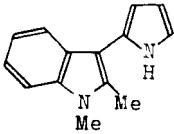
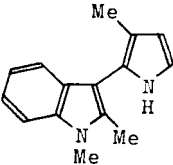
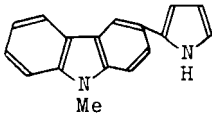
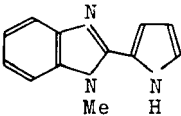
Pyrrole	Structural formula	Yield (%)	b.p., °C (mm Hg) m.p., °C	$d_4^{20}$	$n_D^{20}$	Reference
2-(2-Furyl)-pyrrole		22	m.p., 41			(81KGS1058)
2-(2-Furyl)-1-vinyl-pyrrole		50	b.p., 75–76 (3)	1.0886	1.5977	(81KGS1058)
2-(2-Furyl)-3-methylpyrrole		23	b.p., 103 (3)	0.9674	1.5785	(81KGS1058)
2-(2-Furyl)-3-methyl-1-vinyl-pyrrole		85	b.p., 88 (3)	1.0803	1.5775	(81KGS1058)
2-(2-Thienyl)pyrrole		61	m.p., 75			(85ZOR406)
2-(2-Thienyl)-1-vinylpyrrole		62	b.p., 110–111 (1)	1.0526	1.6350	(85ZOR406)

3-Ethyl-2-(2-thienyl)pyrrole		52	b.p., 125–126 (1)	1.1093	1.6675	(85ZOR406)
3-Ethyl-2-(2-thienyl)-1-vinyl-pyrrole		70	b.p., 116–118 (1)	1.0450	1.5981	(85ZOR406)
3- <i>n</i> -Hexyl-2-(2-thienyl)-1-vinyl-pyrrole		60	b.p., 153–157 (1)	1.0241	1.5698	(85ZOR406)
1,2-Dimethyl-3-(3-isopropyl-2-pyrrolyl)indole		29	m.p., 170–172			(83KGS356)
1-Methyl-2-(3-methyl-1-vinyl-2-pyrrolyl)indole		46	oil			(83TH1)
1,3-Dimethyl-2-(3-methyl-1-vinyl-2-pyrrolyl)indole		35	oil			(83TH1)

(continued)

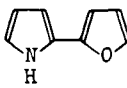
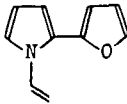
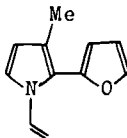
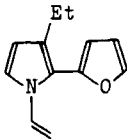
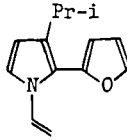
TABLE XVII (continued)

Pyrrole	Structural formula	Yield (%)	b.p., °C (mm Hg) m.p., °C	$d_4^{20}$	$n_D^{20}$	Reference
1-Methyl-3-phenyl-(3-methyl-1-vinyl-2-pyrrolyl)indole		31	oil			(83TH1)
1-Methyl-3-(2-pyrrolyl)indole		35	m.p., 108–110			(83KGS356)
1-Methyl-3-(1-vinyl-2-pyrrolyl)indole		69	m.p., 77–79			(84KGS69)

1,2-Dimethyl-3-(2-pyrrolyl)indole		36	m.p., 165–166	(83KGS356)
1,2-Dimethyl-3-(3-methyl-2-pyrrolyl)indole		31	m.p., 158–160	(83KGS356)
9-Methyl-3-(2-pyrrolyl)carbazole		30	m.p., 134–135	[89ZOR(ip)]
1-Methyl-2-(2-pyrrolyl)benzimidazole		58	m.p., 210	(81KGS1422)

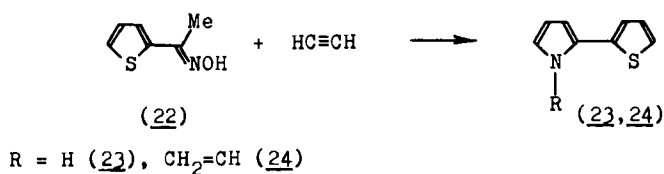
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TABLE XVIII  
TYPICAL UV AND IR SPECTRA OF 2-(2-FURYL)PYRROLES (81KGS1058)

Pyrrole	UV, nm	$\lambda_{\max}$ , (log $\epsilon$ )	IR (cm <sup>-1</sup> )
	198 279	(4.04) (4.25)	595,725,795,887,942,1010,1030,1108,1158,1212,1282, 1500,1620,2930,3120,3430
			595,717,795,877,902,965,996,1020,1070,1085,1155,1180, 1220,1252,1293,1320,1350,1375,1424,1447,1472, 1500,1537,1612,1642,2930,3120,3140
	204 267	(4.10) (4.22)	595,650,730,807,862,895,965,1007,1027,1077,1150,1202, 1230,1305,1372,1387,1417,1485,1507,1567,1646, 2870,2930,3120,3140
	204 270	(4.08) (4.17)	597,665,732,810,862,897,944,965,993,1080,1155,1205, 1231,1270,1315,1370,1382,1415,1460,1480,1505,1612, 1642,2880,2940,2970,3120,3140
	200 265	(4.20) (4.13)	595,665,700,738,807,865,897,970,985,1000,1025,1060, 1080,1160,1205,1240,1315,1370,1385,1415,1470,1480, 1510,1550,1612,1642,2880,2930,2965,3120,3140

diverse modifications. By the reaction of methyl 2-thienyl ketoxime (**22**) with acetone in the presence of potassium hydroxide in DMSO (100–140°C), 2-(2-thienyl)pyrrole (**23**) was prepared in 60% yield. With excess of acetylene 2-(2-thienyl)-1-vinylpyrrole (**24**) is formed (Scheme 13) (77KGS1136).

The reaction was performed in an autoclave under an initial acetylene pressure of 8–15 atm. The IR spectrum of 2-(2-thienyl)-pyrrole (**23**) and its *N*-vinyl derivative (**24**) displays characteristic bands of the thiophene



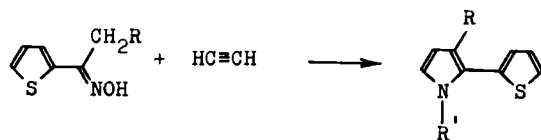
SCHEME 13

(705, 1040, 1515  $\text{cm}^{-1}$ ) and pyrrole (716, 1380, 1470  $\text{cm}^{-1}$ ) rings, *N*-vinyl group bands (598, 850, 935, 1580, 1645  $\text{cm}^{-1}$ ), a multiplet in the region 3075–3140  $\text{cm}^{-1}$  arising from stretching of C—H heterocycles and the *N*-vinyl group. The UV spectrum of 2-(2-thienyl)-1-vinylpyrrole (**24**) [ $\lambda_{\text{max}}$ , nm log ( $\epsilon$ )] includes 200 (4.28), 250 (4.10), 294 (4.04). The first two bands are characteristic of *N*-vinylpyrroles (75KGS1225), the third maximum corresponding to a bathochromic shift of the absorption of the thiophene ring conjugated with the pyrrole ring (77KGS1136).

The  $^{13}\text{C}$ -NMR spectrum of the *N*-vinylpyrrole moiety of pyrrole **24** (ppm) shows peaks at 133.48 ( $\text{C}^2$ ), 111.5 ( $\text{C}^3$ ), 110.34 ( $\text{C}^4$ ), 118.35 ( $\text{C}^5$ ), 130.94 ( $\text{C}-\alpha$ , vinyl), and 98.74 ( $\text{C}-\beta$ , vinyl), which corresponds to the  $^{13}\text{C}$ -NMR spectra of other *N*-vinylpyrroles (75KGS360). The signals 127.16, 126.30 (double intensity) and 125.14 ppm are due to the thienyl carbons. Without proton decoupling, the  $\text{C}^2$  signal appears as a singlet which indicates the presence of 2-thienyl substituent in this position.

In more recent work (85ZOR406), important experimental details concerning heterocyclization of other ketoximes of the thiophene series with acetylene in the MOH/DMSO ( $\text{M} = \text{Li}, \text{K}$ ) system have been reported (Scheme 14).

The reaction of alkyl thienyl ketoximes with acetylene proceeds smoothly at 100–130°C and can be performed under both elevated and atmospheric pressure. Normally, yields of thienylpyrroles are 50–70% (Table XVII). The ratio of pyrroles and their *N*-vinyl derivatives formed in a synthesis can be controlled by the reaction conditions, i.e., time, temperature, and variation of alkali cation. 2-(2-Thienyl)-1-vinylpyrrole is more readily obtained in an autoclave under elevated acetylenic pressure and by heating the reagents (120°C) in the presence of KOH (17–30% of methyl



$\text{M} = \text{Li}, \text{K}; \text{R} = \text{H}, \text{Me}, \text{Et}, \text{n-Pr}, \text{n-Bu}, \text{n-C}_6\text{H}_{13}; \text{R}' = \text{H}, \text{CH}_2=\text{CH}$

SCHEME 14

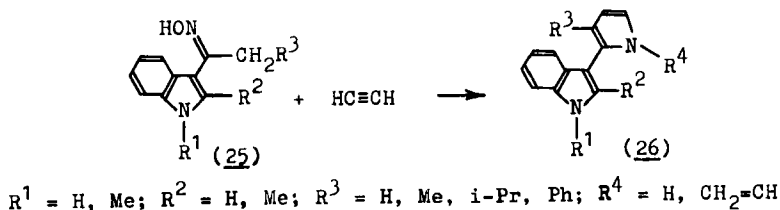


thienyl ketoxime mass) for 3 hr. 2-(2-Thienyl)pyrrole free from its vinyl derivative can conveniently be prepared by use of the LiOH/DMSO pair (100°C, 3 hr, 10–12 atm). In this case, LiOH is employed in an amount of 18% of the ketoxime mass. The yield of 2-(2-thienyl)pyrrole exceeds 60%. The same pyrrole can also be prepared in 47% yield at atmospheric pressure (130–140°C, 7 hr, 30% LiOH). At 110°C, other conditions being equal, no heterocyclization takes place, and the initial ketoxime is recovered. At the same time, in the presence of KOH (60% of the ketoxime mass, 100°C, atmospheric pressure of acetylene, 6.5 hr), this very pyrrole was obtained in 34% yield. Addition of water (10–15% of DMSO mass) when KOH (100%) is used at 100°C inhibits the process of vinylation and allows 2-(2-thienyl)pyrrole to be selectively prepared in 53% yield. The same yield is achieved for 3-ethyl-2-(2-thienyl)pyrrole by heating (100–120°C) *n*-propyl thienyl ketoxime with acetylene (80% KOH, 11% H<sub>2</sub>O, 7 hr) (85ZOR406).

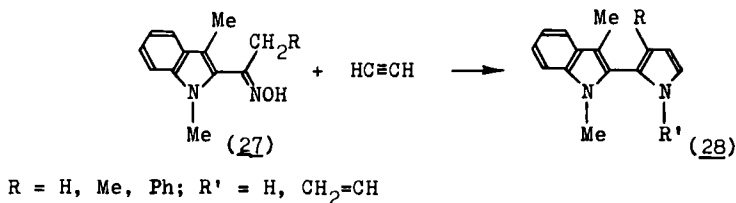
Previously unknown 3-(2-pyrrolyl)indoles (**26**) were obtained in 3–45% yield (Table XVII) by condensation of 3-acylindole oximes (**25**) with acetylene (KOH/DMSO, 100–105°C, acetylene atmospheric pressure, oxime/KOH molar ratio 1 : 1.2, 0.5–5 hr) (Scheme 15) (83KGS356, 83MI3, 83TH1; 84KGS69).

The methyl group in position 2 causes a considerable increase in the rate of vinylation of the 2-methyl-3-(2-pyrrolyl)indole (**26**, R<sup>1</sup> = R<sup>3</sup> = R<sup>4</sup> = H, R<sup>2</sup> = Me). This is due, in the author's opinion, to a distortion of coplanarity of the molecule causing the pyrrole moiety to become more accessible to acetylene attack. Also possible, however, is an enhanced nucleophilicity of the corresponding pyrrolate-anion, owing to the electron-donating effect of the methyl group.

With 2-acylindole oximes (**27**) (Scheme 16) under the same conditions, the vinylation of the 2-(2-pyrrolyl)indoles (**28**) formed becomes the predominant process, and only 2-(1-vinyl-2-pyrrolyl)indoles (**28**, R' = CH<sub>2</sub>=CH) are isolated from the reaction mixture (Table XVII). A decrease in the reaction temperature to 70°C slows down pyrrolization but does not avoid the formation of (*N*-vinylpyrrolyl)indoles (83TH1).



SCHEME 15



SCHEME 16

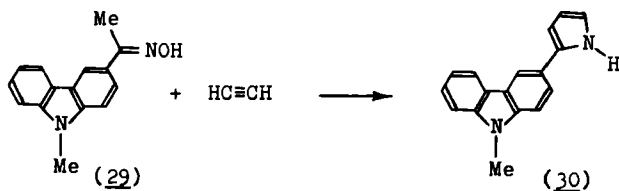
Thus, with a general simple synthetic route to pyrrolyl indoles, a whole class of pyrrole compounds, completely inaccessible not long ago, has been worked out.

The reaction of 3-acetyl-9-methylcarbazole oxime (29) with acetylene (Scheme 17) allows 9-methyl-3-(2-pyrrolyl)carbazole (30) to be prepared in 30% yield under the following conditions:  $65^\circ\text{C}$ , 2 hr, equimolar oxime 29/KOH ratio, 20-fold excess DMSO with respect to 29 (by mass), initial acetylene pressure of 12 atm (autoclave) [90ZOR(ip)].

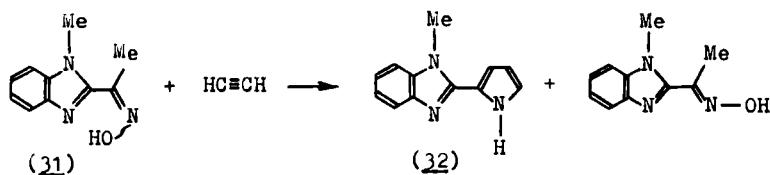
In the  $\text{LiOH}/\text{DMSO}$ -catalyzed reaction ( $70^\circ\text{C}$ , 3 hr, autoclave), the yield of pyrrolyl carbazole 30 is about 3%, whereas when carried out at atmospheric pressure ( $120^\circ\text{C}$ , 5 hr), the reaction leads to pyrrolylcarbazole 30 in 15% yield.

9-Methyl-3-(2-pyrrolyl)carbazole is isolated from a strongly resinified reaction mixture by chromatography on  $\text{Al}_2\text{O}_3$  ( $\text{Et}_2\text{O}$ ) as a gray-green powder, m.p.  $134\text{--}135^\circ\text{C}$  (Table XVII). The  $^1\text{H-NMR}$  spectrum of this compound ( $\text{CDCl}_3$ , ppm) shows 8.46 (NH, broadened), 6.85 (d,  $\text{H}^5$ ), 6.52 (q,  $\text{H}^4$ ), 6.32 (d,  $\text{H}^3$ ), 3.81 (s, 9- $\text{CH}_3$ ), 8.12, 8.03, 7.40, 7.23 (carbazole protons). The IR spectrum (KBr,  $\text{cm}^{-1}$ ) has the following bands: 3370, 3030, 3090, 1480, 1590, 1600, 2830, 2905. Thus the possibility of a one-pot synthesis of pyrrolylcarbazoles via oximes of accessible acylcarbazoles has been demonstrated.

In the reaction of a mixture of *E*- and *Z*-isomers of 1-methyl-2-acetylbenzimidazole oxime (31) in the  $\text{KOH}/\text{DMSO}$  system ( $90\text{--}95^\circ\text{C}$ , atmospheric acetylene pressure, mass oxime 31/KOH/DMSO ratio 1:1:20, 3 hr), the pyrrole ring is formed only from the *Z*-isomer. Recovered oxime



SCHEME 17



SCHEME 18

is pure *E*-isomer which does not react with acetylene under the same conditions (Scheme 18) (81KGS1422).

The yield of 1-methyl-2-(2-pyrrolyl)benzimidazole (32) is 58% based on the consumed *Z*-isomer (Table XVII). Its  $^1\text{H-NMR}$  spectrum (DMSO- $\text{D}_6$ , ppm) shows 3.96 (s, NMe), 6.28 (m,  $^3\text{H}$ ), 6.83 (m,  $\text{H}^4$ ), 7.03 (m,  $\text{H}^5$ ), 7.23, and 7.56 (benzene protons). The less coplanar *Z*-oximate anion is likely to encounter less sterical hindrance upon acetylene molecule attack.

#### D. OXIMES OF CYCLIC AND HETEROCYCLIC KETONES

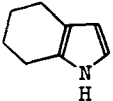
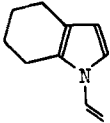
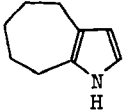
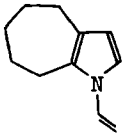
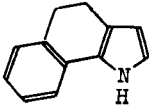
1-Vinyl-4,5,6,7-tetrahydroindole (2) was the first pyrrole to be obtained from ketoximes and acetylene (Scheme 1) (73ZOR2205, 74MI2; 75MI1, 75MI2, 75MIP1; 77BRP1463228, 77GEP2543850; 78MIP1, 78USP4077975; 82JAP1090993). Later, conditions which permit the reaction to be stopped at the stage of formation of 4,5,6,7-tetrahydroindole (1) were found (78MIP1).

When the reaction is carried out under pressure, the yields of pyrroles 1 and 2 are 74–81 and 93%, respectively (Table XIX). Under atmospheric or slightly excess pressure (1.2–1.5 atm), they are 50 and 90%, respectively (78MIP1, 79KGS197). The synthesis of 4,5,6,7-tetrahydroindole (1) from cyclohexanone oxime and acetylene at atmospheric pressure (the yield is 45% when based on the initial oxime and 56% on the oxime reacted) has already been included in the manual (88MI1). Principle features and experimental details of this synthesis have been discussed (79KGS197).

The synthesis of *NH*- and *N*-vinyltetrahydroindoles (1,2) is successfully performed with the cyclohexanone oxime/acetylene molar ratio 1 : (2–5) at 90–140°C with bases (alkali metal hydroxides and alkoxides) taken in amounts of 10–50% of cyclohexanone oxime mass, serving as reaction catalysts. The reaction is catalyzed by potassium, rubidium, and tetrabutylammonium hydroxides (78MIP1).

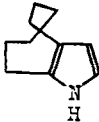
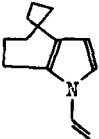
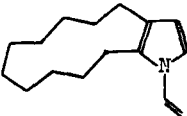
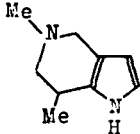
Pyrrolization takes place in both polar aprotic solvents (sulfoxides and more reluctantly, amidophosphates) and mixtures thereof with non-polar and low polarity solvents (dioxane, benzene) taken in a volume ratio to cyclohexanone oxime of (1–25) : (1–10). The use of mixed DMSO–

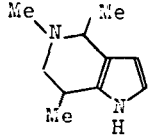
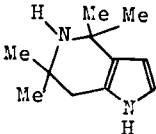
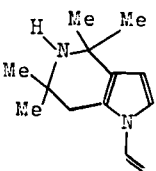
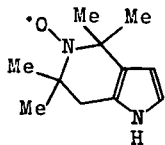
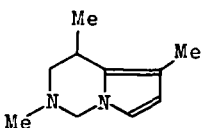
TABLE XIX  
REPRESENTATIVES OF CONDENSED PYRROLES PREPARED FROM OXIMES OF CYCLIC KETONES

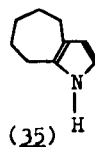
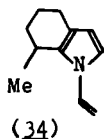
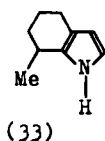
Compound	Structural formula	Yield (%)	b.p., °C (mm Hg) m.p., °C	$d_4^{20}$	$n_D^{20}$	Reference
4,5,6,7-Tetrahydroindole		74	m.p., 50			(79KGS197)
1-Vinyl-4,5,6,7-tetrahydroindole		93	b.p., 85–86 (3)	1.0010	1.5562	(79KGS197)
4,5,6,7,8-Pentahydro-1 <i>H</i> -cyclohepta[ <i>b</i> ]pyrrole		79	m.p., 102			(76MIP1)
1-Vinyl-4,5,6,7,8-pentahydro-1 <i>H</i> -cyclohepta[ <i>b</i> ]pyrrole		93	b.p., 73–74 (1)	0.9937	1.5560	(84MI1)
4,5-Dihydrobenzo[ <i>g</i> ]indole		70	m.p., 109			(78ZOR1119)

(continued)

TABLE XIX (continued)

Compound	Structural formula	Yield (%)	b.p., °C (mm Hg) m.p., °C	$d_4^{20}$	$n_D^{20}$	Reference
4,5,6,7,8,9-Hexahydro-1 <i>H</i> -cycloocta[ <i>b</i> ]pyrrole		60	b.p., 57–58 ( $5 \cdot 10^{-2}$ )			[89IZV(ip)]
1-Vinyl-4,5,6,7,8,9-hexahydro-1 <i>H</i> -cycloocta[ <i>b</i> ]pyrrole		~100	b.p., 64.5–66 ( $3 \cdot 10^{-2}$ )	0.9809	1.5512	[89IZV(ip)]
1-Vinyl-4,5,6,7,8,9,10-11,12,13-decahydro-1 <i>H</i> -cyclododeca[ <i>b</i> ]pyrrole		~100	b.p., 114–116 ( $5 \cdot 10^{-2}$ )		1.5472	[90IZV(ip)]
5,7-Dimethylpyrrolo[3,2- <i>c</i> ]piperidine		16	m.p., 155–157			(87KGS937)

4,5,7-Trimethylpyrrolo[3,2-c] piperidine		22	m.p., 139–140			(87KGS937)
4,4,6,6-Tetramethylpyrrolo[3,2-c] piperidine		24	m.p., 128–129 b.p., 103 (3)			(88KGS350)
1-Vinyl-4,4,6,6-tetramethylpyrrolo [3,2-c]piperidine		90	m.p., 25–27	0.9805	1.5303	(88KGS350)
4,4,6,6-Tetramethyl-5-oxylpyrrolo (3,2-c)piperidine		65	m.p., 143–144			(88KGS350)
2,4,5-Trimethyl-1,2,3,4- tetrahydropyrrolo[1,2- c]pyrimidine		15 16				(87KGS1286) (87TH1)



dioxane solvents allows the reaction to be carried out selectively, i.e., either tetrahydroindole (with DMSO content of about 5–10%) or 1-vinyltetrahydroindole (in pure DMSO) can be prepared.

The  $^1\text{H}$ -NMR spectrum of 1-vinyl-4,5,6,7-tetrahydroindole (73ZOR-2205) contains two resolved multiplets (4 protons each) at 1.47 ppm (protons at  $\text{C}^5$  and  $\text{C}^6$ ) and 2.24 ppm (protons at  $\text{C}^4$  and  $\text{C}^7$ ) and five signals with various multiplicities in the 4.10–6.60 ppm region: 6.43 ( $^3\text{J}$  8.9,  $^3\text{J}$  15.6,  $^4\text{J} \approx ^5\text{J}$  0.4 Hz); 4.21 ( $^2\text{J}$  0.8 Hz); 4.66; 6.54 ( $^3\text{J}$  3.0 Hz); 5.76.

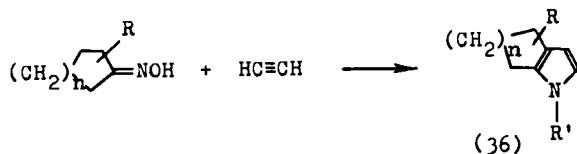
Under the conditions of proton noise decoupling, the  $^{13}\text{C}$ -NMR spectrum of 1-vinyl-4,5,6,7-tetrahydroindole (73ZOR2205) displays 10 signals of which six are present in the region characteristic of aromatic and olefinic  $^{13}\text{C}$  nuclei (ppm): 128.41, 125.21, 116.86, 112.46, 107.65, 92.75, 21.79, 21.49, 21.42, 19.92.

2-Methylcyclohexanone and suberone (cycloheptanone) oximes correspondingly give 7-methyl-4,5,6,7-tetrahydroindole (33, yield 70%), its *N*-vinyl derivative [34, yield 80% (75MI1)], and 4,5,6,7,8-pentahydro-1*H*-cyclohepta[*b*]-pyrrole [35, yield 79% (76MI1; 80KGS1299)] (Table XIX).

Recently [89IZV(ip)] the effect of the cycloalkanone oxime ring size on their pyrrolization rate under the action of acetylene in the KOH/DMSO system at 86°C and atmospheric pressure has been examined (Scheme 19).

In Fig. 6, a family of typical kinetic curves for cyclohexanone oxime are presented, which imply that pyrrole formation involves an intermediate, evidently, potassium oximate.

The rate constant for various stages of cycloalkanone oxime pyrrolization were calculated according to Scheme 20, taking into account a constant concentration of acetylene.



$n = 1-4, 8; \text{R} = \text{H};$

$n = 2; \text{R} = 5\text{-Me}, 7\text{-Me}; \text{R}' = \text{H}, \text{CH}_2=\text{CH}$

SCHEME 19

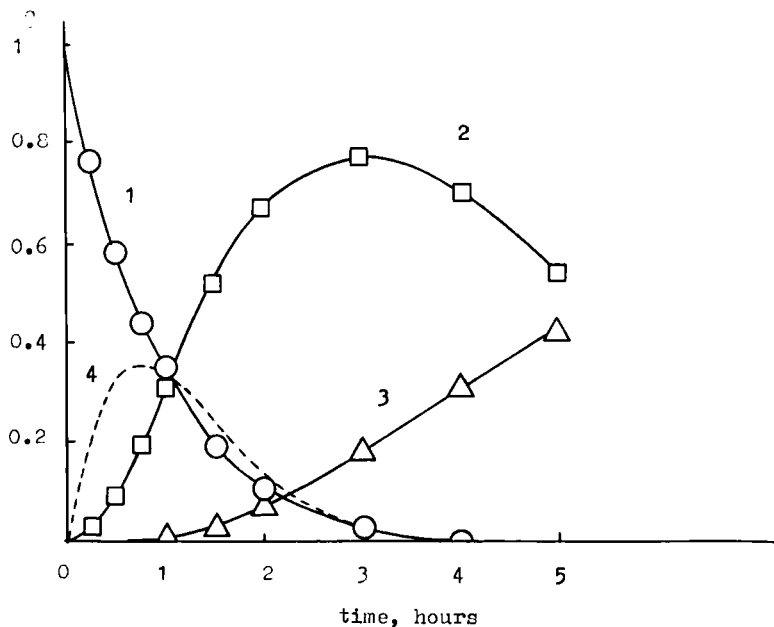


FIG. 6. Typical kinetics of the reaction of cyclohexanone oxime with acetylene: 1, cyclohexanone oxime; 2, 4,5,6,7-tetrahydroindole; 3, 1-vinyl-4,5,6,7-tetrahydroindole; 4, an intermediate. Reaction conditions: DMSO, 86°C,  $P_{C_2H_2}$  720 mm Hg, concentration of KOH and cyclohexanone oxime 0.47 mol/L;  $C = C_t/C_0$ , where  $C_0$  and  $C_t$  are the initial and present concentration of components, respectively.

At the stage of pyrrole vinylation ( $k_2$ ), the influence of the ring size and the methyl substituents is negligible (Table XX). The largest ring size effect ( $k_1$  is decreased by one order) is observed at the stage of transformation of the intermediate into pyrrole on going from a six-membered ring to a 12-membered one. With cyclopentanone oxime ( $n = 1$ ), this stage does not take place at all.

Pyrroles **36** with  $n = 4, 8$  have been isolated and characterized (Table XIX). These include 4,5,6,7,8,9-hexahydro-1*H*-cycloocta[*b*]pyrrole (yield 60%, optimal synthesis time about 3 hr), which shows a reduced stability as compared with other pyrroles of this series ( $n = 2, 3, 8$ ). Nevertheless, the reason for the unsuccessful attempt to synthesize this compound from cyclooctanone oxime and acetylene [87JCS(P1)2829] is not very clear.

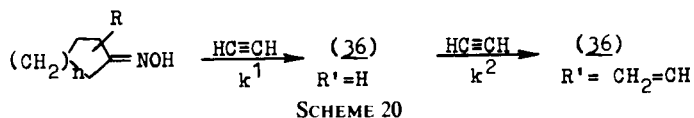




TABLE XX  
RATE CONSTANTS<sup>a</sup> OF PYRROLIZATION<sup>b</sup> OF  
CYCLOALKANONE OXIMES ( $k_1$ ) AND VINYLATION<sup>b</sup>  
OF THE PYRROLES FORMED ( $k_2$ )<sup>c</sup>

Oxime ring size, $n$	$k_1 \cdot 10^5$	$k_2 \cdot 10^5$
1	reaction is complicated by side-processes	
2	25	1.9
2 (2-Me)	25	1.8
2 (4-Me)	26	1.9
3	2.9	1.3
4	17	1.5
8	2.1	1.1

<sup>a</sup> First order constants ( $s^{-1}$ ).

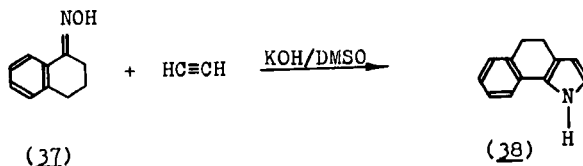
<sup>b</sup>  $T = 86^\circ C$ ,  $P_{C_2H_2} = 720 \pm 10$  mm Hg.

<sup>c</sup> From reference [89IZV(ip)], see also Scheme 20.

Numerous attempts to obtain pyrroles annelated with a cyclopentane ring, starting from cyclopentanone oxime, were unsuccessful. Despite widely varying conditions, it was possible to detect (by NMR or IR spectroscopy) only trace amounts of pyrroles in the products (84MI1).

Ketone oximes of the hydronaphthalene series can successfully be transformed into pyrroles. Thus, 4,5-dihydrobenzo[g]indole (**38**) was prepared in one stage (yield 70%) from  $\alpha$ -tetralone oxime (**37**) and acetylene (Scheme 21) (78ZOR1119).

This provides a simple route to difficult-to-obtain compounds of the 4,5-dihydrobenzo[g]indole series, which are rather promising in the search for new bioactive substances and dyes. 4,5-Dihydrobenzo[g]indole (see Table XIX) was isolated by column chromatography ( $Al_2O_3$ ,  $Et_2O$ /hexane 1 : 2) as colorless crystals that turn blue in air. The  $^1H$ -NMR spectrum of pyrrole **36** ( $CDCl_3$ , ppm) shows 7.1 m (four benzene protons); 6.8 t and 6.0 t (two pyrrole protons); and 2.8 m (four protons in positions 4 and 5). The IR spectrum shows the characteristic bands of the pyrrole and benzene moieties ( $cm^{-1}$ ): 695, 730, 765, 1510, 1560, 1580, 1610, 3040, 3050, 3100, 3390, and 3430.



SCHEME 21

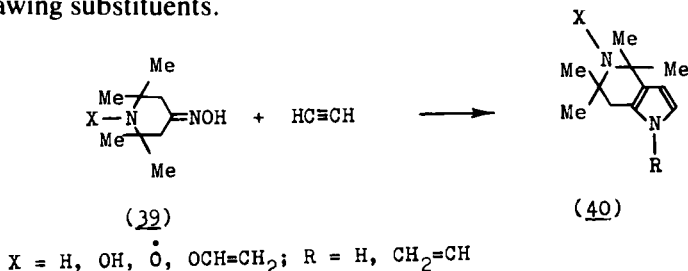
Some features of the behavior of 2,2,6,6-tetramethyl-4-piperidone oxime (**39**) ( $X = H$ ) and its oxidized derivatives ( $X = OH$ ,  $X = \dot{O}$ ) in the reaction with acetylene in KOH/DMSO (Scheme 22) are discussed (88KGS350) along with experimental details dealing with the synthesis of new pyrrolo[3,2-*c*]piperidines (**40**), previously reported either briefly (84MI2) or in general (86ZC41).

The oxime **39** bearing a nitroxyl group ( $X = \dot{O}$ ) can be converted to the corresponding azaindole **40** without affecting the free-radical center (yield 65%, nonoptimized conditions). It follows that (i) the presence of the nitroxyl function in ketoximes does not impede their pyrrolization by the reaction with acetylene in a superbase medium, and (ii) the acetylene-involved pyrrolization of ketoximes in the presence of superbase does not show any clearly defined radical stage, otherwise the nitroxyl center would have acted as a spin trap, thus inhibiting the reaction.

The ketoximes **39** with  $X = OH$  or  $\dot{O}$  are converted to pyrroles more readily than the nonoxidized form (**39**,  $X = H$ ). Thus, if the former at 50–60°C form azaindole **40** ( $X = \dot{O}$ ) in a yield of 48 and 65%, respectively, the latter at 90–95°C, other conditions being equal, is converted to azaindole **40** ( $X = H$ ) in a yield as low as 24%.

When reacted with acetylene in the KOH/DMSO system at 50–60°C, 1-hydroxy-2,2,6,6-tetramethyl-4-piperidone oxime (**39**,  $X = OH$ ) forms azaindole **40** with a nitroxyl group ( $R = H$ ;  $X = \dot{O}$ , yield 48%), implying an oxidation–reduction process takes place under the reaction conditions. At elevated temperature (105°C) and with excess acetylene, oxime **39** ( $X = OH$ ) is converted to 1-vinylazaindole **40** with  $X = H$ . Therefore, under more harsh conditions, the KOH/DMSO system acts as a reductant with respect to the nitroxyl radical.

In the course of redox pyrrolization of the oxime **39** with  $X = OH$ , the hydroxyl group in position 5 is vinyllated to a slight extent to form 1-vinyl-5-vinyloxy-4,4,6,6-tetramethyl-4,5,6,7-tetrahydro-5-azaindole (**40**,  $X = OCH=CH_2$ ). This was the first example of nucleophilic addition of hydroxylamine to a triple bond not activated by strong electron-withdrawing substituents.



SCHEME 22

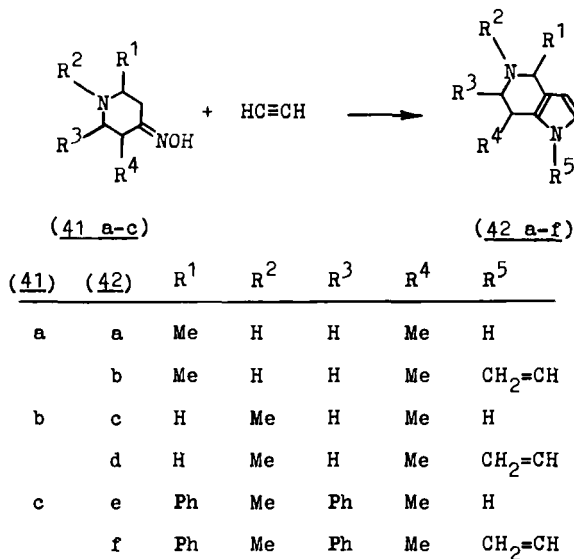
It is not possible (88KGS350) to obtain 1-vinylazaindole **40** having a nitroxyl group from oximes **39** ( $X = OH, \dot{O}$ ). In these two cases, only the corresponding *NH*-pyrrole ( $R = H, X = \dot{O}$ ) is formed at 50–65°C. When the temperature rises (95°C), the oxime **39** ( $X = \dot{O}$ ) is converted to 1-vinylazaindole **40** ( $R = CH=CH_2$ ) with the loss of the radical center ( $X = H$ ). This may be an indication of the vinylation of pyrroles in the KOH/DMSO system to involve a one-electron stage.

As far as purely preparative results are concerned, the highest yield (90%) of the *N*-vinylazaindole **40** ( $R = CH_2=CH, X = H$ ) was achieved by use of the oxime **39** ( $X = H$ /KOH/DMSO molar ratio of 1:3:43 (105°C, 8 hr). At 95°C, under all other equal conditions, the same *N*-vinylazaindole is formed in 87% yield for 5.5 hr, whereas at the equimolar oxime/KOH ratio (90–95°C, 6 hr), a mixture of *NH*-azaindole **40** ( $R = H, X = H$ ) (yield 24%) and the starting oxime (**39**,  $X = H$ ) was obtained. The reaction of the same oxime with acetylene under pressure (14 atm, 100°C, 3 hr, equimolar oxime/KOH ratio) is accompanied by considerable resinification, decreasing the yield of *N*-vinylazaindole **40** ( $R = CH_2=CH, X = H$ ) to 38%. The *NH*-azaindole **40** ( $R = H, X = \dot{O}$ ) is the only reaction product if the oxime **39** ( $X = OH$ ) reacts with acetylene at 50–60°C (88KGS350).

In the IR spectra of *NH*-azaindoles **40** ( $X = H, \dot{O}$ ) (KBr pellets, Nujol) the NH group stretch is observed at 3280  $cm^{-1}$  (intermolecular hydrogen bond). In the spectrum of a diluted solution ( $CCl_4, 3 \cdot 10^{-3}$  mol/L), two bands are present, one (3458  $cm^{-1}$ ) corresponds to a free group of the *NH*-pyrrole ring [3495  $cm^{-1}$  in pyrrole (52JCP145)], the other weak band at 3330  $cm^{-1}$  is the piperidine NH vibration (3347  $cm^{-1}$  [56AC(R)165]). The constancy of the NH frequency (3330  $cm^{-1}$ ) in the spectra of *N*-vinylazaindole **40** ( $R = CH_2=CH, X = H$ ) in both film and diluted solutions ( $CCl_4$ ) indicates that the piperidine ring NH group screened by methyls cannot form intermolecular hydrogen bonds. The vinyl group of this azaindole occurs in the IR spectrum as bands at 1645 ( $\nu C=C$ ), 865 ( $\delta CH_2=$ ), and 3100  $cm^{-1}$  ( $\nu CH_2=$ ). The bands 1380, 1490, and 1550  $cm^{-1}$  in the IR spectra of azaindoles **40** are typical of the pyrrole ring (84MI1).

The UV spectrum of the *N*-vinylazaindole **40** ( $R = CH_2=CH, X = H$ ) shows two bands [ethanol,  $\lambda_{max} \log(\epsilon)$ ]: 202 nm (4.10) and 247 nm (4.10), and this corresponds closely to 1-vinyl-4,5,6,7-tetrahydroindole (2) (84MI1). The UV spectra of the two *NH*-azaindoles **40** ( $R = H, X = H, \dot{O}$ ) contains bands with  $\lambda_{max} (\log \epsilon)$  at 213 nm (3.89) and 216 nm (3.93) and bear resemblance to the spectrum of 4,5,6,7-tetrahydroindole (1) (81MI5).

The *NH*-azaindole **40** with  $X = \dot{O}$  is paramagnetic. Its electron spin resonance (ESR) spectrum (in DMSO) shows a characteristic triplet with a 1:1:1 intensity and the hyperfine splitting constant  $a_N = 16.04$  Oe.

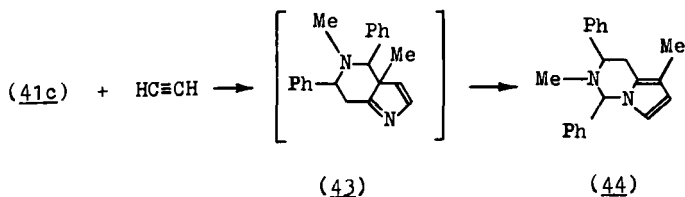


SCHEME 23

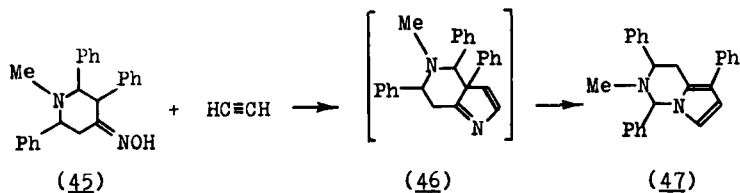
The  $^1\text{H}$ -NMR spectrum of this azaindole displays only indistinct broad signals, the positions of which corresponds to those in the spectra of nonparamagnetic azaindoles ( $X = \text{O}$ ). Analogously, the oximes **41**, when treated with acetylene (KOH/DMSO,  $\text{C}_2\text{H}_2$ , atmospheric pressure, 90–100°C, 4–5 hr), form azaindoles **42** (Scheme 23, Table XIX) (87KGS937).

The two pyrrolo-piperidine stereoisomers **42a** and **42c** were isolated in the individual form (m.p., 139–140 and 155–157°C, respectively). Analysis of the spin–spin coupling constants in  $^1\text{H}$ -NMR spectra indicates that the piperidine conformation is a half-chair with a transdiequatorial arrangement of methyl groups at  $\text{C}^4$  and  $\text{C}^7$ .

Oxime **41c** gives a compound in 2% yield (87KGS937), which was first assigned a 3*H*-pyrrole structure, 3*aH*-3*a*,5-dimethyl-4,6-diphenylpyrrolo-[3,2-*c*]piperidine (**43**) (Scheme 24). The formation of this compound is explained by involvement of the piperidine fragment methine group in the cyclization (see Section IV.C).



SCHEME 24

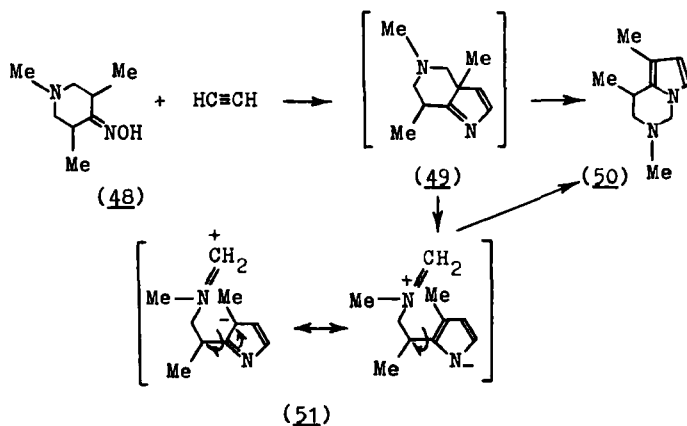


SCHEME 25

Heterocyclization of oxime **45** with acetylene under similar conditions (87KGS937) formed only 3*H*-pyrrole **46** in small yield (Scheme 25). However, it became clear later (87TH1) that the products **43** and **46** were pyrrolo[1,2-*c*]pyrimidines **44** and **47** (Scheme 24 and 25).

This interesting mechanism of heterocyclization of piperidine oximes with acetylene leading to pyrrolo[1,2-*c*]pyrimidines was further discussed by Prostavok and co-workers (87KGS1286). 1,3,5-Trimethylpiperidin-4-one oxime (**48**) formed 2,4,5-trimethyl-1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidine (**50**) in 16% yield, evidently, due to aromatization of the intermediate 3*H*-pyrrole (**49**) (Scheme 26).

The  $^1\text{H}$ -NMR spectrum of pyrrolo[1,2-*c*]pyrimidine **50** ( $\text{CDCl}_3$ , ppm) (87KGS1286) is 1.28 (d, *J* 6.9 Hz, 4- $\text{CH}_3$ ), 2.08 (s, 5- $\text{CH}_3$ ), 2.42 (s, 2- $\text{CH}_3$ ), 2.56 (dd, *J* 12.1, 6.7 Hz,  $\text{H}^3$  axial), 2.82 (ddd, *J* 12.1, 5.5, 1.1 Hz,  $\text{H}^3$  equatorial), 3.10 (m,  $\text{H}^4$ ), 4.27 (dd, *J* 9.5, 1.1 Hz,  $\text{H}^1$  equatorial), 4.56 (d, *J* 9.5 Hz,  $\text{H}^1$  axial), 5.96 (d, *J* 2.5 Hz,  $\text{H}^6$ ), 6.40 (d, *J* 2.5 Hz,  $\text{H}^7$ ). Its  $^{13}\text{C}$ -NMR spectrum ( $\text{CDCl}_3$ , ppm) is 127.1, 115.1, 113.4, 109.5 (pyrrole cycle), 68.5 ( $\text{C}^1$ ), 59.2 ( $\text{C}^3$ ), 41.6 ( $\text{NCH}_3$ ), 26.4 ( $\text{C}^4$ ), 19.12, 11.5 (4- $\text{CH}_3$ , 5- $\text{CH}_3$ ).



SCHEME 26

The rearrangement (Scheme 26) seems to be due to heterolysis of the  $C^{3a}-C^4$  bond and rotation about the  $C^7-C^{1a}$  bond with subsequent formation of zwitterionic intermediate **51**.

This new interesting reaction could be the basis for a simple general synthetic route to difficult-to-obtain pyrrolo[1,2-*c*]pyrimidines.

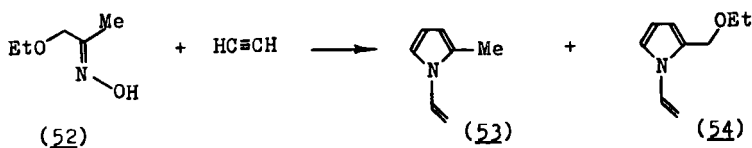
## E. FUNCTIONAL KETOXIMES

### 1. Oximes of Hydroxyalkyl Ketones

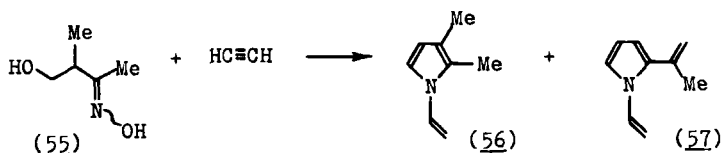
Extention of the reaction of ketoximes with acetylene to oximes of hydroxyalkyl ketones can lead to the synthesis of inaccessible, functionally substituted pyrroles and *N*-vinyl derivatives. However, the methyl  $\alpha$ - and  $\beta$ -hydroxyalkyl ketoximes used by Trofimov *et al.* (80ZOR410) appeared to react with acetylene in the KOH/DMSO system in an abnormal way.

As a rule, cleavage of the oxygen-containing radical R at the C—O bond takes place, and a mixture of simpler pyrroles is formed in low yield. Although of little preparative interest, these results nevertheless shed light on some features of this reaction as a whole. 1-Hydroxy-2-propanone oxime, the simplest member of the series of ketoximes studied, is unstable and undergoes complete resinification under normal conditions of the reaction of ketoximes with acetylene. Its ethyl ether, 1-ethoxy-2-propanone oxime (**52**) is more stable and, when reacting with excess acetylene, gives an anomalous product, 2-methyl-1-vinylpyrrole (**53**) in a yield of up to 15%, which often exceeds the yield of the expected 2-(ethoxymethyl)-1-vinylpyrrole (**54**) (Scheme 27).

Unlike methyl alkyl ketoximes from which the pyrrole ring is preferentially constructed from the alkyl methylene group (78KGS54), oxime **52** utilizes only the methyl group for this. In one case only (80ZOR410), the  $^1\text{H-NMR}$  spectrum of the reaction products indicated signals tentatively assigned to the second expected isomer, 3-ethoxy-2-methyl-1-vinylpyrrole.



SCHEME 27



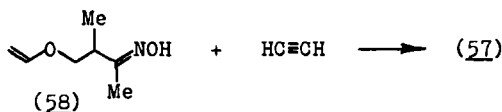
SCHEME 28

The thin-layer chromatography (TLC) monitoring of the reaction (Scheme 28) leads to a conclusion that the "anomalous" 1-vinyl-2-methylpyrrole (53) is a secondary product from the pyrrole (54). When reacting with excess acetylene in an autoclave at 100°C, 1-hydroxy-2-methyl-3-butanone oxime (55) gives two anomalous products, 2,3-dimethyl-1-vinylpyrrole (56), which was also reported (78IZV2426), and 2-(1-propenyl-2)-1-vinylpyrrole (57) in 20 and 8% yields respectively (Scheme 28).

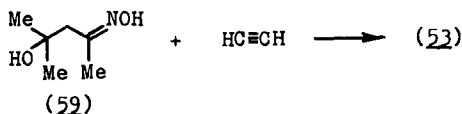
Among the reaction products, the oxime of methyl ethyl ketone was found. Under atmospheric pressure (flow system) and at a lower temperature (80°C), the same oxime (55) affords nonvinylated 2,3-dimethyl- and 2-(1-propenyl-2)pyrroles in low yield along with a larger amount of resin (~50%). In a run without acetylene carried out under even harsher conditions (100–110°C, 7 hr, atmospheric pressure), over 80% of the oxime 55 was recovered.

The vinyl ether of the oxime 55, 2-methyl-1-vinyloxy-3-butanone oxime (58) with excess acetylene also gives the pyrrole 57, however, none of the pyrrole 56 is formed in this case (Scheme 29). Upon distillation, pyrrole 57 polymerizes readily, which is one reason for its low yield.

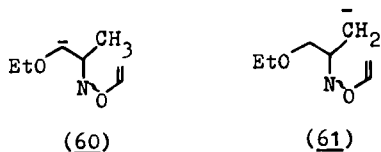
2-Hydroxy-2-methyl-4-pentanone oxime (59) reacts with acetylene to form 2-methyl-1-vinylpyrrole (53) in a yield of about 20% (Scheme 30).



SCHEME 29



SCHEME 30



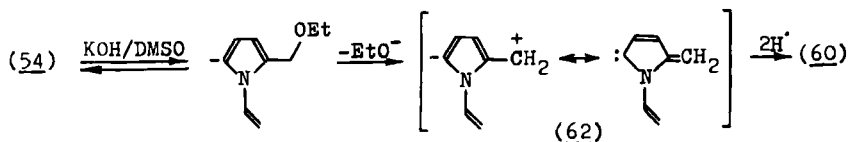
SCHEME 31

The results obtained confirm the conclusions (75KGS360; 78KGS54) concerning the important role played by carbanion bearing charge at the  $\alpha$ -carbon relative to the oxime function on the first stage of pyrrole ring formation. It is from this position that regioselectivity of the reaction (Scheme 27) leading to the pyrrole **54** rather than its isomer, 3-ethoxy-2-methyl-1-vinylpyrrole, can be explained. The intermediate carbanion **60** is destabilized compared with the alternative carbanion **61** because of repulsion of the negative charge from lone electron pairs of the oxygen atom. Therefore the reaction proceeds via the more stable carbanion **61**, affording the pyrrole **54** (Scheme 31).

The formation of 2-methyl-1-vinylpyrrole **53** in the reaction (Scheme 27) is more difficult to rationalize. Taking into account that this pyrrole appears in the reaction mixture as 2-(ethoxymethyl)-1-vinylpyrrole **54**, it is quite reasonable to suggest elimination of the ethoxy group from the latter, which is supported because ethanol is identified among the reaction products.

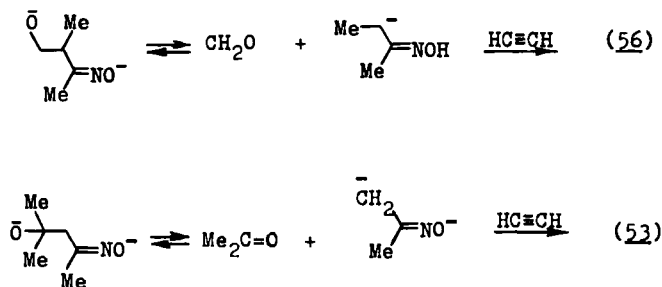
The elimination of ethanol seems to start with deprotonation of the  $\alpha$ -position of the pyrrole **54** under the action of superbases. The carbenoid intermediate **62** formed is then reduced (Scheme 32). The reducing properties of the KOH/DMSO system have been observed (88KGS350).

The formation of pyrroles **54** and **57** is likely to be a result of decomposition of the oximes **55** and **59** in the form of dianion by analogy with retroaldol condensation (Scheme 33). As far as the formation of pyrrole **57** (Schemes 28 and 29) is concerned, this seems to result from  $\beta$ -elimination of water and vinyl alcohol molecules from the oximes **55** and **58** respectively or from the corresponding intermediate 2-hydroxy(vinyloxy)propyl-1-vinylpyrroles.



SCHEME 32





SCHEME 33

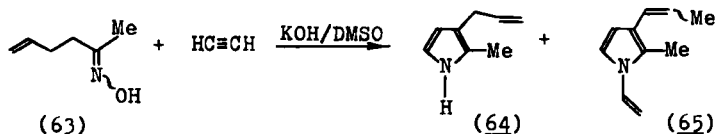
The fact that most of the oxime **55** is recovered from a blank reaction without acetylene favors the elimination in the resulting pyrroles rather than in the starting oximes (80ZOR410).

## 2. Oximes of Olefinic Ketones

Pyrroles with unsaturated substituents are known as deficient starting materials for the synthesis of diverse functional derivatives of pyrrole. The method of building up the pyrrole ring from ketoximes and acetylene with a simultaneous introduction of a vinyl group to the nitrogen atom proved to be useful in this case as well.

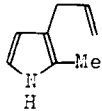
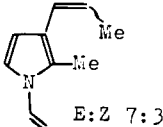
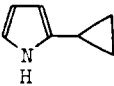
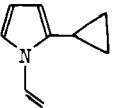
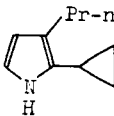
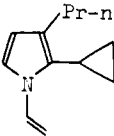
The one-stage transformation of 3-butenyl-1-methyl ketoxime (**63**) to 2-methyl-3-(2-propenyl-1)pyrrole (**64**) and 2-methyl-3-(1-propenyl-1)-vinylpyrrole (**65**) (Scheme 34) (82TL5063) is typical and demonstrates two essential features of this version of the reaction: the reaction either can be stopped selectively at the stage of pyrrole ring formation without vinylation onto the N—H bond and prototropic isomerization of the alkenyl, or it can form an *N*-vinylpyrrole in which the double bond of the alkenyl is shifted into conjugation with the pyrrole ring.

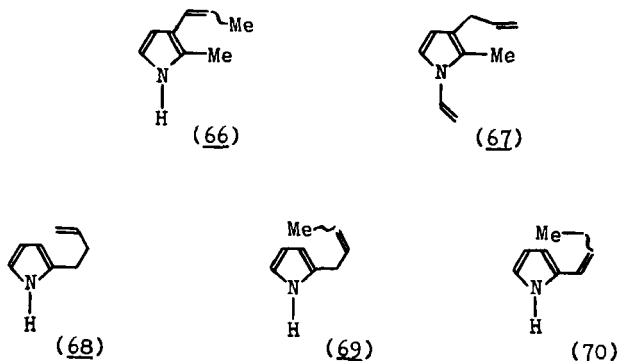
The nonvinylation pyrrole **64** with nonisomerized alkenyl radicals can be obtained at the reaction temperature not exceeding 100°C by heating no more than 1 hr with a slight excess of acetylene under 3–7 atm. The synthesis of this pyrrole can also be performed under atmospheric pressure by passing acetylene through the reaction mixture upon stirring. In



SCHEME 34

TABLE XXI  
REPRESENTATIVES OF ALKENYL AND CYCLOPROPYL PYRROLES DERIVED FROM ALKENYL AND CYCLOPROPYL KETOXIMES

Pyrrole	Structural formula	Yield (%)	b.p., °C (mm Hg)	$d_4^{20}$	$n_D^{20}$	Reference
2-Methyl-3-(2-propenyl-1)-pyrrole		30	90 (8)	0.8956	1.5158	(82TL5063)
2-Methyl-3-(1-propenyl-1)-1-vinyl-pyrrole		80	98-99 (5)	0.9254	1.5717	(82TL5063)
2-Cyclopropylpyrrole		7			1.5371	(88ZOR1788)
2-Cyclopropyl-1-vinyl-pyrrole		10		0.9792	1.5394	(88ZOR1788)
2-Cyclopropyl-3- <i>n</i> -propylpyrrole		24				(88ZOR1788)
3- <i>n</i> -Propyl-2-cyclo-propyl-1-vinylpyrrole		64				(88ZOR1788)



the latter case, the reaction should be carried out until trace amounts of other pyrroles (**65**–**67**) are detected (TLC, GLC).

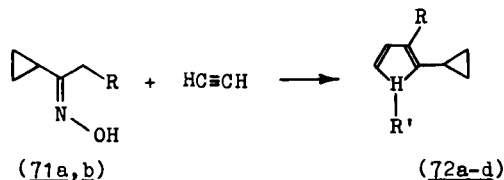
The pyrroles **66** and **67** normally appear in the reaction mixture together with the pyrroles **64** and **65**, but their separation is tedious. At an elevated temperature (110°C) and with approximately 10-fold excess acetylene under 10–14 atm for 3 hr, both isomerization and vinylation take place leading to the pyrrole **65** (a mixture of *E*- and *Z*-isomers) as the only isolable reaction product (Table XXI).

The reaction proceeds regiospecifically at up to 100°C, and neither the pyrroles **68**–**70** nor their *N*-vinyl derivatives are found in the reaction mixture, i.e., under these conditions only the CH<sub>2</sub> group of 3-butenyl-1 radical adjacent to the oxime function is incorporated into the pyrrole ring (see also Section III.F).

This implies a stereospecific contribution of the *E*-form of the ketoxime **63** to pyrrole ring formation since the latter is the major configuration of this ketoxime. The fact that the yield of pyrrole **65** (80%) can exceed the *E*-form content (70%, <sup>1</sup>H NMR) is explained by ready *E* ⇌ *Z* isomerization of ketoximes of this type (68T3347; 78KGS54). Under more severe conditions, the methyl group of ketoximes is also involved in pyrrole ring formation (see Section III.F) and, consequently, pyrroles **68**–**70** can be formed on further increasing the reaction temperature, displacing the equilibrium towards the *Z*-form. However, this rationalization of the regioselectivity of the reaction is not the only one: equilibration between *O*-vinyl intermediates is now a likely alternative (see Sections III.F and IV.B).

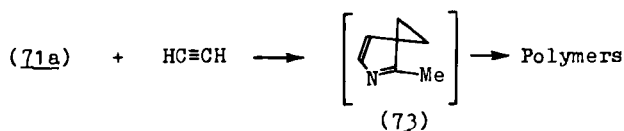
### 3. Oximes of Cyclopropyl Ketones

The cyclopropylpyrroles (**72a–d**), an almost unknown family of pyrroles with high prospects in the search for biologically active compounds and



(71)	(72)	R	R'
a	a	H	H
b	b	n-Pr	H
	c	H	(H <sup>A</sup> )(H <sup>B</sup> )C=C(H <sup>C</sup> )
	d	n-Pr	(H <sup>A</sup> )(H <sup>B</sup> )C=C(H <sup>C</sup> )

SCHEME 35

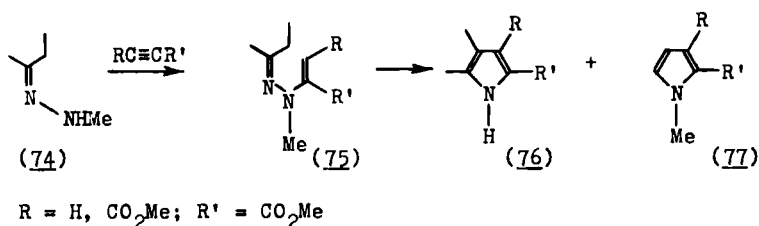


the synthesis of heterocycles, have been prepared (88ZOR1788) in one stage from alkyl cyclopropyl ketoximes (**71a,b**) and acetylene (KOH/DMSO, 80–95°C, 5–6 hr, atmospheric C<sub>2</sub>H<sub>2</sub> pressure) (Scheme 35). Non-optimized yields of the pyrroles **72a–d** range within 7–64% (Table XXI).

The low yields (7–10%) of pyrroles **72a,c** (R = H) seem to be caused by competing annelation at the CH of the cyclopropane ring, which should lead to the strained unstable 3*H*-pyrrole **73** which has not been isolated as yet. The spectra of pyrrole **72d** are typical. The <sup>1</sup>H-NMR spectrum (CDCl<sub>3</sub>, ppm): 0.61 m, 0.88 m (CH<sub>2</sub> in cyclopropyl), 0.95 t (CH<sub>3</sub> in *n*-Pr), 1.52 m (CH in cyclopropyl and β-CH<sub>2</sub> in *n*-Pr), 2.46 t (α-CH<sub>2</sub> in *n*-Pr), 4.54 dd (H<sup>B</sup> J<sub>BC</sub> 9.0, J<sub>AB</sub> 0.8 Hz), 5.98 d (H<sup>A</sup>, J<sub>45</sub> 2.5 Hz), 6.85 d (C<sup>5</sup>), 7.26 dd (H<sup>C</sup>), 7.96 dd (H<sup>A</sup>, J<sub>AC</sub> 15.0 Hz). The IR spectrum of this pyrrole (cm<sup>-1</sup>) contains 700 (pyrrolic ω<sub>C–H</sub>), 810, 890 (ω<sub>C–H</sub> in NCH=CH<sub>2</sub>), 1470, 1565 (pyrrolic ν<sub>C–H</sub>), 1615 (ν<sub>C=C</sub> in NCH=CH<sub>2</sub>), 3085 (ν<sub>C–H</sub> in NCH=CH<sub>2</sub>), 2855, 2910, 2950, 3000 (ν<sub>C–H</sub> in cyclopropyl).

#### 4. Derivatives and Analogs of Ketoximes

It would be attractive from both mechanistic and preparative standpoints to obtain pyrroles by condensation of acetylene with ketoxime derivatives or analogs, e.g., their ethers or hydrazones, i.e., to realize the



SCHEME 36

expected analogs of the reaction in question. However first attempts (80KGS1299) undertaken in this line failed.

Later, French scientists (74BCF1147) made good progress by using methylhydrazones (74) and methyl esters of propiolic and acetylenedicarboxylic acids instead of acetylene. They obtained mixtures of the corresponding 4- and 4,5-methoxycarbonyl substituted pyrroles (76) and their *N*-methyl derivatives (77) in 5–45% yield (Scheme 36). The reaction involves the intermediate *N*-vinylhydrazones (75).

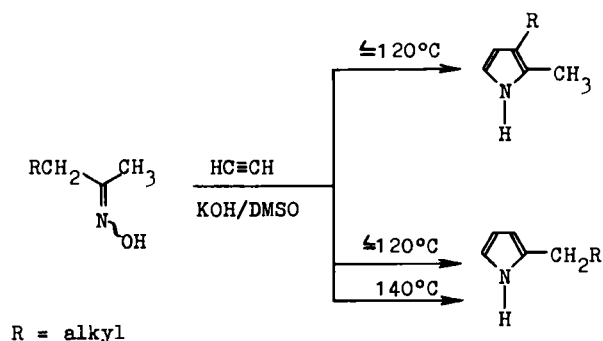
This demonstrates once more the essential differences between the reactivity of unsubstituted acetylene and acetylenes with especially strong electron-withdrawing substituents.

## F. REGIODIRECTION OF THE KETOXIME PYRROLIZATION

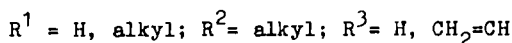
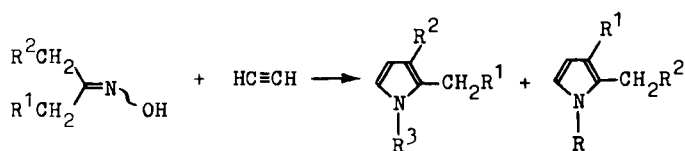
The ketoximes containing only tertiary or aromatic radicals in any combination do not form pyrroles when reacting with acetylene in the presence of superbases (79MI2; 80KGS1299). In the case of ketoximes with secondary alkyl radicals, 4*H*-2-hydroxy-2,3-dihydropyrroles or 3*H*-pyrroles are formed (see Sections IV.B,C).

With unsymmetrical alkyl methyl ketoximes, when competition between the methyl and methylene group is possible, at moderate temperature (up to 120°C) the pyrrole ring is being built up regiospecifically, i.e., only utilizing the methylene group (78KGS54, 80KGS1299, 81MI4). At 140°C, however, the relative content of the second isomeric pyrrole (built up with the participation of methyl) can attain 50% (Scheme 37).

Since the ketoximes exist mainly in the *E*-configuration (68T3347; 76MI1), it is clear that, similar to the Beckmann rearrangement (54MI1), the reaction proceeds by involving the group in the anti-position with respect to the hydroxyl. With increasing temperature, the configuration equilibrium is shifted towards the *Z*-isomer, and regiospecificity of the reaction is broken. Unsymmetrical dialkyl ketoximes in the heterocyclization with acetylene can give two isomeric pyrroles (Scheme 38).



SCHEME 37

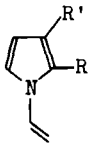


SCHEME 38

For a better understanding of the reaction mechanism and an optimal preparative use of this reaction, it is necessary to know (i) which of two ketoxime groups, methyl or methylene (when  $R^1 = H$ ), is more favorable in building up the pyrrole ring, (ii) whether there are any differences in the reactivity of the two methylene groups (when  $R^1 = R^2 = \text{alkyl}$ ) belonging to different  $n$ -alkyl radicals, and (iii) whether the reaction conditions affect the ratio of isomeric pyrroles. The answers to these questions have been found in studying the pyrrolization of a number of unsymmetrical dialkyl ketoximes with acetylene and  $KOH/DMSO$  under the conditions affording  $N$ -vinylpyrroles (78KGS54). The isomer ratio was determined by GLC and  $^1H$ -NMR spectroscopy.

As Table XXII illustrates, at  $120^\circ C$  the methyl alkyl ketoximes react with acetylene at exclusively the alkyl methylene group, regardless of the structure (iso or normal) of its remaining moiety to form the only isomer. An increase in the temperature breaks the reaction regiospecificity so that at  $140^\circ C$ , the formation of pyrroles at the expense of the methyl group takes place in amounts of 20–50%, i.e., quite acceptable for preparative separation, although the total yield drops. Thus, by adjusting the reaction conditions, it is possible to change its direction and obtain not only 2,3-dialkylsubstituted pyrroles, but also pyrroles free of substituents in position 3 with various alkyls in position 2. Both methylene groups of two

TABLE XXII  
YIELD AND RATIO OF REGIOISOMERS OF 1-VINYLPYRROLES



OBTAINED FROM UNSYMMETRICAL KETOXIMES

$$\begin{array}{c} \text{R}'\text{CH}_2 \\ \diagup \\ \text{C} = \text{NOH (78KGS54)} \\ \diagdown \\ \text{RCH}_2 \end{array}$$

Pyrrole		120°C <sup>a</sup>		140°C <sup>b</sup>	
R	R'	Content of mixture (%)	Total yield (%)	Content of mixture (%)	Total yield (%)
Me	Me <sup>c</sup>	99	73	65	33
H <sup>c</sup>	Et	1		35	
Me	<i>n</i> -Pr <sup>c</sup>	100	83	79	61
H <sup>c</sup>	<i>n</i> -Bu	trace amounts		21	
Me	<i>i</i> -Pr <sup>c</sup>	100	87	50	36 <sup>d</sup>
H <sup>c</sup>	<i>i</i> -Bu	trace amounts		50	
Me	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	100	76	70	35
H <sup>c</sup>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	trace amounts		30	
Et	<i>n</i> -Pr <sup>c</sup>	50	75	50	50
Me <sup>c</sup>	<i>n</i> -Bu	50		50	

<sup>a</sup> 30 % KOH of ketoxime mass, ketoxime/DMSO ratio 1 : 10, initial acetylenic pressure 10–14 atm, 3 hr.

<sup>b</sup> 10 % KOH of ketoxime mass, ketoxime/DMSO ratio 1 : 4, other conditions the same as at 120°C.

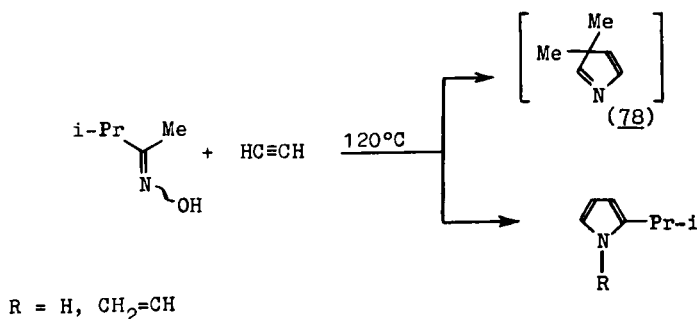
<sup>c</sup> R and R' radicals in the corresponding oximes.

<sup>d</sup> Ketoxime/DMSO ratio was 1 : 8.

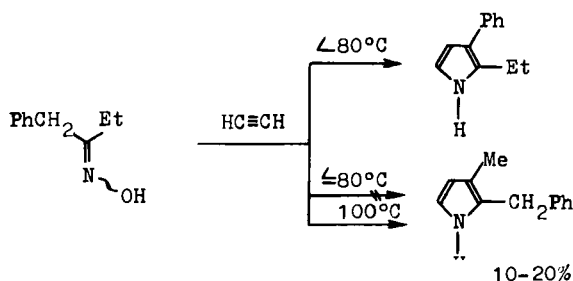
different alkyls of normal structure, (e.g., in butyl ethyl ketoxime) show similar reactivity: even at 120°C, both isomeric pyrroles are formed in approximately equal amounts (Table XXII).

With methyl *i*-propyl ketoxime (competition of the CH<sub>3</sub> and CH groups) only 2-*i*-propylpyrrole and its vinyl derivative can be isolated in 10 and 15% yield, respectively. Under these conditions (Table XXII), the 3H-pyrrole **78** appears to be unstable (Scheme 39).

If two different methylene groups are competing as in benzyl ethyl ketoxime, for example, the competition is won by that placed in the anti-position to the hydroxyl, i.e., the benzyl methylene group in this case. The regiospecificity observed at a temperature below 80°C is broken with increasing temperature (80KGS1299) (Scheme 40).



SCHEME 39



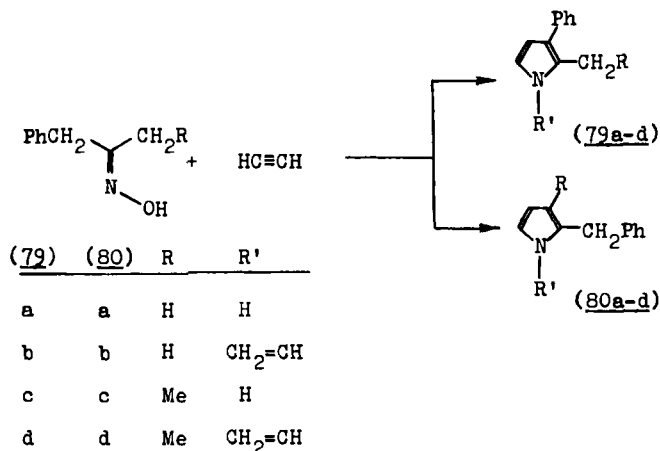
SCHEME 40

Further analysis of the regiodirection of the reaction was undertaken with benzyl methyl and benzyl ethyl ketoximes (88KGS193). The former was pure *E*-isomer and the latter consisted of *E*- and *Z*-isomers in a ratio of 45 : 55. As shown by Trofimov *et al.* (82KGS193), at room temperature the isomer ratio is not affected much by solvents. Upon heating for an hour in nitrobenzene, benzyl methyl ketoxime is partially converted to the *Z*-isomer, the content of which increases with temperature (according to  $^1\text{H}$ -NMR data) from 1% at  $25^\circ\text{C}$  to 36% at  $150^\circ\text{C}$ .

In the  $\text{KOH}/\text{DMSO}$  system, benzyl methyl ketoxime is converted to a mixture of *E*- and *Z*-isomers (74 : 26) upon a short-term heating ( $80^\circ\text{C}$ , 10 min); further temperature rise ( $150^\circ\text{C}$ ) has practically no effect on the isomer ratio. Consequently, the *Z*-form content of benzyl methyl ketoxime within the 26–36% range (depending on medium) seems to be close to the equilibrium value. Unlike benzyl methyl ketoxime, the isomer ratio of benzyl ethyl ketoxime evidently corresponds to the equilibrium value even in the initial sample, since upon heating in nitrobenzene ( $150^\circ\text{C}$ ) or in the  $\text{KOH}/\text{DMSO}$  mixture ( $170^\circ\text{C}$ ), it does not change much.

During the interaction of benzyl methyl and benzyl ethyl ketoximes with acetylene, one can expect in each case the formation of two isomeric





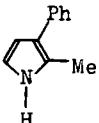
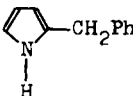
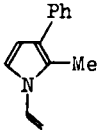
SCHEME 41

pyrroles (**79a**, **79c** and **80a**, **80c**) and *N*-vinyl derivatives thereof (**79b**, **79d** and **80b**, **80d**), which differ by the position and structure of ring substituents (Scheme 41).

As shown by GLC analysis and <sup>1</sup>H NMR spectra, however, in the reaction of benzyl methyl ketoxime (R = H, Scheme 41) with excess acetylene (100°C, KOH), only the 2-methyl-3-phenyl-1-vinylpyrrole (**79b**) is formed. The regiospecificity is not broken even under harsher conditions (120°C): no 2-benzyl-1-vinylpyrrole (**80b**) was detected in the reaction mixture. An analogous result was obtained when the reaction was carried out in LiOH/DMSO (120°C), which catalyzes the stage of vinylation less actively. Under these conditions, the *N*-vinylpyrrole (**79b**) and its nonvinyolated precursor (**79a**) are formed in approximately equal amounts (1 : 1.2). Their regioisomers (**80a** and **80b**) are absent in the reaction mixture. A peculiarity of the reaction catalyzed with LiOH/DMSO is more clearly expressed than with KOH: deoxygenation, i.e., the formation of original ketones which is readily identified in the reaction mixture by IR spectroscopy (the 1710 cm<sup>-1</sup> band, which is absent in the spectra of oximes). With higher concentrations of reagents and base (oxime 9% and KOH 3.5% of the reaction mixture mass instead of 7 and 2.5%, respectively) and at 120°C, it was possible to isolate and spectrally characterize (Tables XXIII and XXIV) 2-benzylpyrrole (**80a**) as well, which means that the methyl group also starts reacting under these conditions. These results indicate that benzyl methyl ketoxime reacts with acetylene predominantly via the methylene group of the benzyl radical.

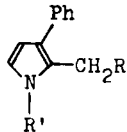
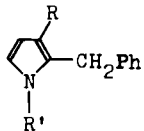
At 100°C, benzyl ethyl ketoxime with excess acetylene in the KOH/DMSO system gives two *N*-vinylpyrrole isomers (**79d** and **80d**). As the

TABLE XXIII  
COMPARISON OF IR SPECTRA OF ISOMERIC PYRROLES OBTAINED FROM BENZYL  
METHYL KETOXIME<sup>a</sup>

Pyrrole	Formula number	$\nu$ , $\text{cm}^{-1}$
	(79a)	515, 650, 700, 714, 764, 897, 956, 1030, 1086, 1256, 1375, 1445, 1510, 1604, 2855, 2916, 3025, 3380, 3426
	(80a)	407, 540, 717, 767, 885, 957, 1028, 1092, 1108, 1378, 1452, 1495, 1580, 1604, 2858, 2930, 2960, 3025, 3060, 3983, 3390, 3426
	(79b)	505, 590, 620, 662, 700, 715, 765, 862, 910, 957, 1032, 1072, 1130, 1147, 1248, 1300, 1320, 1372, 1380, 1437, 1458, 1500, 1560, 1578, 1604, 1642, 2952, 2922, 2952, 3030, 3055, 3080

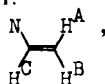
<sup>a</sup> From reference (82KGS193).

TABLE XXIV  
COMPARISON OF <sup>1</sup>H-NMR SPECTRA OF ISOMERIC PYRROLES (79,80) OBTAINED FROM BENZYL  
METHYL AND BENZYL ETHYL KETOXIMES<sup>a</sup>

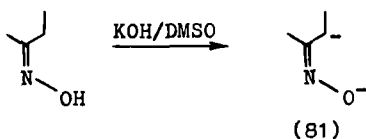
Pyrrole	R	R'	Chemical shifts <sup>b</sup> (ppm)							
			H <sup>A</sup>	H <sup>B</sup>	H <sup>C</sup>	H <sup>3</sup>	H <sup>4</sup>	H <sup>5</sup>	Me	CH <sub>2</sub>
	H	H					6.14	6.35	2.05	
	H	H				5.83	5.95	6.42		3.85
79b	H	CH <sub>2</sub> =CH	5.00	4.57	6.85		6.15	6.85	2.27	
79d	Me	CH <sub>2</sub> =CH	5.03	4.59	6.86		6.14	6.82	1.10	2.70
80d	Me	CH <sub>2</sub> =CH	4.85	4.36	6.60		5.93	6.80	2.00	3.90

<sup>a</sup> From reference (82KGS193), see also Scheme 41.

<sup>b</sup> Vinyl group protons are designated as follows



$J_{AB}$  0.8,  $J_{AC}$  15.8,  $J_{BC}$  8.9 Hz; for all pyrroles  $J_{45}$  2 Hz.



temperature rises, the fraction of vinylpyrrole **82d** formed with the participation of the benzyl group is considerably reduced (from 85% at 100°C to 45% at 150°C). Further elevation of the reaction temperature causes resinification and a sharp decrease of the total yield of *N*-vinylpyrroles **79d**, **80d**). At 60–80°C, the major reaction product is the nonvinylated pyrrole **79c**. At 80°C, for example, a mixture of isomeric pyrroles **79c** and **80c** was obtained in a ratio of 5.7 : 1 (<sup>1</sup>H-NMR data). Thus, benzyl ethyl ketoxime also reacts with acetylene mainly via the benzyl methylene group.

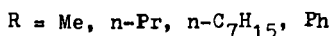
When a mixture of *E*- and *Z*-isomers of 2-acetyl-1-methylbenzimidazole oxime reacts with acetylene in the KOH/DMSO system (Scheme 18, Section III.C) the synthesis of pyrroles is effected only via the *Z*-isomer (81KGS1422).

Previously (78KGS54; 82KGS193), when no facts concerning isolation of *O*-vinylloximes from the acetylene–ketoxime reaction were reported, the explanations for the regiodirection of pyrrolization were based on the assumption that the *O*,*C*-dianions **81** resulted from deprotonation of a ketoxime, which many researchers believe (75TL3889; 76S237, 76S238, 76TL1439) are the key intermediates of the reaction.

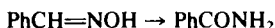
Since the stability of the dianion **81** is critically dependent on its configuration, the emphasis was laid on analyzing this question (78KGS54; 80KGS1299; 82KGS193; 84MI1). At present, however, there are convincing evidences for the formation of pyrroles from ketoximes and acetylene to involve the intermediate *O*-vinylloxime (see Section IV.A and VI). Consequently, the regiospecificity observed might be the result of the thermodynamically controlled equilibrium shift towards the more stable disubstituted (and extra conjugated, if benzyl ketoximes are the case) functional olefin. It is probable, too, that deprotonation from the side of the electron-rich vinyloxy group is kinetically unadvantageous.

### G. WHY DO ALDOXIMES NOT FORM PYRROLES?

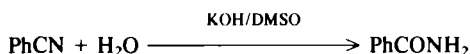
In attempts (76IZV690; 80KGS1299; 81MI4) to extend the pyrrole synthesis from ketoximes and acetylenes to aldoximes, the oximes of both aliphatic and aromatic aldehydes have been found to readily convert to the corresponding nitriles upon moderate heating (60–140°C) in KOH/DMSO.



The yield of nitriles from aliphatic aldoximes under suitable conditions (reaction time 1–5 hr, KOH 0.1–0.3 mol per 1 mol of aldoxime) can attain 92% (76IZV690). At 140°C under the same conditions, benzaldoxime converts to benzamide in 25% yield.



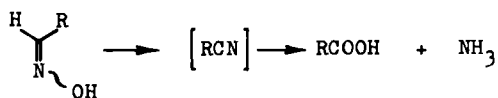
When the reaction is carried out in boiling DMSO, no significant gain in the yield of benzamide (30%) is observed. Since under these conditions the primary dehydration of aldoximes is evident, the formation of benzamide is most likely to result from hydration of the intermediate benzonitrile rather than by the Beckmann rearrangement scheme.



The fact that under the same conditions acetophenone oxime does not form amides, but remains intact, also provides evidence against the classical Beckmann rearrangement. The conditions found can be employed for preparing amides from nitriles and aldoximes, especially when the latter contain fragments unstable to acids. In the absence of DMSO, benzaldoxime is dehydrated with alkali only at the boiling point (200°C).

Although the dehydration of aldoximes in the presence of bases is well known, it has not been developed much in the preparative aspect. It has been reported (54MI1) that on heating oximes with oxides and hydroxides, ammonia is evolved and carbonyl compounds are partially regenerated. Occasionally, nitriles can be prepared by treating of *O*-alkyl oximes with potassium amide in liquid ammonia (54MI1). The formation of the nitrile was observed when camphor oxime was treated with organo-magnesium compounds (73TL1061).

The transformation of aldoximes into nitriles under the action of alkalies was described by Hantzsch as far as the end of the last century. As established by him, *E*-thiophenaldoxime and *E*-mesitylenaldoxime gave nitriles when heated with soda (89ICB36) or hot alkali (895CB744), respectively. In 1908, Reissert (08CB3810) observed the formation of nitrile from *o*-nitrobenzaloxime under the action of hydroxide ions. Later on, Brady *et al.* (25JCS2427, 26JCS1918) examined this transformation in more detail, including *Z*-*o*-iodobenzaldoxime as an example, too.



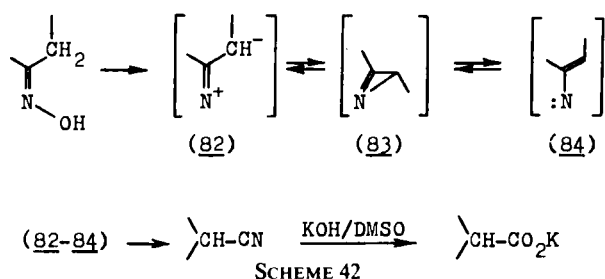
R = Ph, 2-furyl

At that time, however, these reactions were not brought to the level of preparative synthesis of nitriles. The main obstacle seemed to be further transformation of the nitriles to acids. In some cases, upon treating aldoximes with alkalis, it was not at all possible to fix nitriles since they immediately converted to acids. The *anti(E)*-isomers exhibit an enhanced reactivity in these cases. Thus, when boiled in 2 *N* NaOH, *E*-aldoximes are slowly converted to a mixture of the corresponding carboxylic acids and *syn(Z)*-aldoximes to evolve ammonia (36JA1227). Under these conditions for 4 hr the *E*- and *Z*-benzaldoximes undergo 13 and 48% conversion to form benzoic acid in 10 and 38% yield, respectively. Analogously, the *E*- and *Z*-oximes of furfural, under the same conditions for 1.5 hr, are converted to furan-2-carboxylic acid in 33 and 62% conversion and 18 and 49% yield, respectively.

Hydrolysis of the nitriles formed to amides and/or acids in 2 *N* NaOH at 65–100°C was also observed by Brady and Jarrett (50JCS1227), who investigated transformations of acylated halobenzaldehydes in the presence of alkalis.

The formation of carboxylic acid salts from aldoximes via intermediate nitriles and amides also takes place beyond any doubt in the KOH/DMSO system, although this was not mentioned by Trofimov *et al.* (76IZV690). This seems to be responsible for unsuccessful attempts to obtain the corresponding nitrile from furfurole oxime in the system just mentioned. Later on (84MI1), in addition to the results published (76IZV690), it has been reported that the dehydration of aldoximes to nitriles could be performed under far milder conditions without an autoclave (60–100°C) atmospheric pressure). Acetylene does not affect this process very much. However, in no case have pyrroles or *O*-vinylloximes been unambiguously identified among the reaction products (GLC, NMR, IR spectroscopy). It is only in particular runs that the mixture of products, consisting mainly of nitrile and aldoxime, gives a positive qualitative reaction for pyrrole.

By analogy with the dehydration of aldoximes in the KOH/DMSO system, which certainly involves abstraction of the proton nearest to the oxime function, in the case ketoximes, one can expect 1,3-dehydration which leads to unstable intermediates such as the 1,3-dipole **82**, azirine **83**, vinylnitrene **84** or nitrile, or the stable rearrangement product of one of them (Scheme 42).



Under these reaction conditions, nitriles can readily transform to the salts of the corresponding carboxylic acids. This may account for the loss of ketoxime without visible signs of resinification occasionally observed in the synthesis of pyrroles from ketoximes and acetylene or its equivalents, i.e., vinyl halides and dihaloethanes (see Section V.B).

#### IV. Intermediates and Side Products

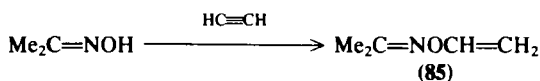
In the course of systematic development of heterocyclization of ketoximes with acetylene into pyrroles, the formation of *O*-vinylloximes (79IZV695; 80KGS1299; 81MI4, 81UK248), 4*H*-hydroxy-2,3-dihydropyrroles (83KGS276, 83MI5), 3*H*-pyrroles (85KGS1573), dipyrrolethanes (88ZOR1789), 1-(2-methylthiovinyl)pyrroles (86MI2), pyridines (80KGS-1299; 81MI4, 81UK248) and  $\alpha$ -acetylenic alcohols (80KGS1299; 81MI4, 81UK248) has been found to take place in special cases.

##### A. *O*-VINYL KETOXIMES

As shown in the review by Trofimov and Mikhaleva (80KGS1299), the results of the preceding research dealing with the interaction of oximes and acetylenes are contradictory to a certain extent. Thus, according to Sheradsky (70TL25), ketoximes add their hydroxyl group to dimethyl acetylenedicarboxylate to form *O*-vinyl derivatives. At the same time (67AG722, 67T2641; 69CB2336, 69CB2346; 70TL25; 73CRV283; 74M15), it follows that the reactions of this type lead to *N*-vinyl nitrones (67AG722; 69CB2336, 69CB2346; 73CRV283) or to *N*-vinyl zwitterionic intermediates (67T2641; 73CRV283, 74M15), which further add the second acetylene molecule thus converting to oxazole (67AG722; 69CB2336, 69CB2346) or pyridine derivatives (67T2641; 73CRV283).

The synthesis of *O*-vinylacetoxime by direct vinylation of acetoxime with calcium carbide in an aqueous medium, reported by Pivnenko (70ZOR2146), failed to be reproduced (75ZOR1141). Under these conditions, a symmetrical collidine was obtained instead of *O*-vinylacetoxime (75ZOR1141, 75KGS1427).

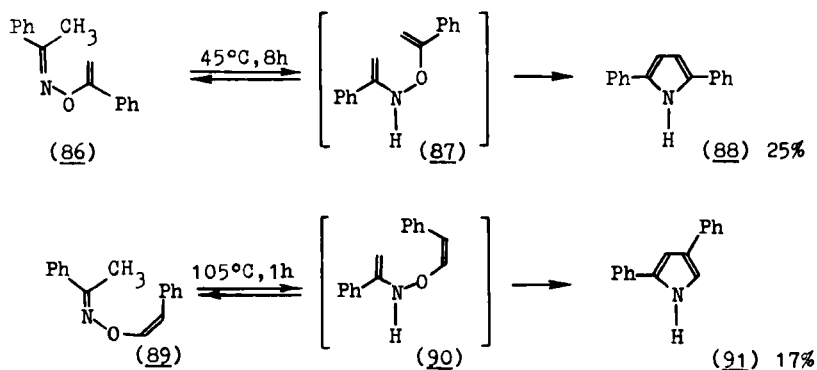
The direct acetylene-assisted vinylation of acetoxime was first reported by Trofimov *et al.* (79IZV695). The reaction occurs in the presence of 30% KOH (of the oxime mass) at 110°C in DMSO with a steady removal of the *O*-vinylacetoxime (**85**) from the reaction zone by a fast acetylene stream.



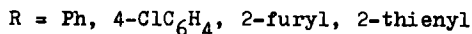
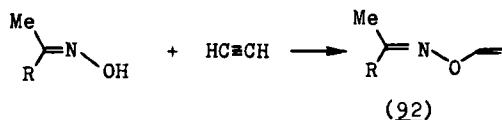
The yield of vinylated acetoxime is not high (to 10%). The formation of pyrroles, the products of intermediate *O*-vinloxime rearrangement (83KGS273), remains the major reaction pathway under these conditions. Although no 2-methylpyrrole was detected (GLC control) in a resin obtained by the thermolysis of *O*-vinylacetoxime (**85**), this pyrrole was found in a small quantity (~5%) in the products of decomposition of *O*-vinylacetoxime in KOH/DMSO.

Later on, the same results were obtained with  $\alpha$ - and  $\beta$ -*O*-(phenylvinyl)acetophenone oximes (**86,89**), which readily rearranged to the corresponding pyrroles **88** and **91** in KOH/DMSO, while under the conditions of noncatalytic pyrolysis (150°C, 10 min), they resinified to give only trace amounts (TLC) of the expected pyrroles (Scheme 43).

Special studies aimed at the development of a preparative synthesis of *O*-vinloximes have been undertaken. It turned out that this could be achieved only with alkyl aryl and alkyl hetaryl ketoximes (84M11) if the



SCHEME 43



SCHEME 44

latter reacted with acetylene under the initial pressure 10–12 atm in the KOH/DMSO system at 40–60°C (Scheme 44).

Potassium hydroxide is taken in an equimolar ratio with respect to the initial ketoxime. The yield of *O*-vinylloximes (92) amounts to 65% with 52–77% conversion of ketoximes. At present, this seems to be the only suitable route to *O*-vinylloximes bearing no substituent in the vinyl group. The IR and <sup>1</sup>H-NMR spectra of *O*-vinylloximes resemble those of vinyl ethers in the position and shape of characteristic bands and proton signals of the vinyloxy group (80KGS1299).

When heated (100°C) in KOH/DMSO, the *O*-vinylaryl(hetaryl) ketoximes (92) convert to the corresponding pyrroles in a yield up to 96% for only 1.5 hr (83KGS273). Under analogous conditions, *O*-vinylacetoxime undergoes mainly resinification (yield of 2-methylpyrrole 5%). In the absence of the superbase, only traces of 2-phenylpyrrole fixed by TLC are formed from acetophenone oxime *O*-vinyl ether. At 150°C, the thermolysis of the same *O*-vinylloxime is completed in 1 hr, but resin eventually is formed (84MI1), whereas 2-phenylpyrrole is detected as a faint spot on the TL-chromatogram.

Thus, the superbase-catalyzed rearrangement of *O*-vinylloximes is an intermediate stage in the formation of pyrroles in their synthesis from ketoximes and acetylene in KOH/DMSO (81MI4, 83KGS273, 84MI1). This was finally confirmed by Yurovskaya *et al.* in examples with acylindole oximes and acetylene (83KGS356, 83MI3, 83TH1; 84KGS69) as well as with acetophenone oxime and phenylacetylene (84KGS1077). The authors made use of this rearrangement to develop a convenient two-stage one-pot procedure for a selective preparation of *NH*-pyrroles free of their *N*-vinyl derivatives: *O*-vinylloxime prepared in advance from ketoxime and acetylene at 40–70°C was then converted with out isolation to pyrrole by heating the reaction mixture to 100°C, acetylene supply being ceased in this stage.

It is worthy to stress that the rearrangement of *O*-vinylloximes of aromatic and heteroaromatic ketones to pyrroles proceeds smoothly only in the KOH/DMSO system, which is quite different from the noncatalyzed pyrolysis of *O*-1,2-di(carbomethoxy)vinylloximes (70TL25).



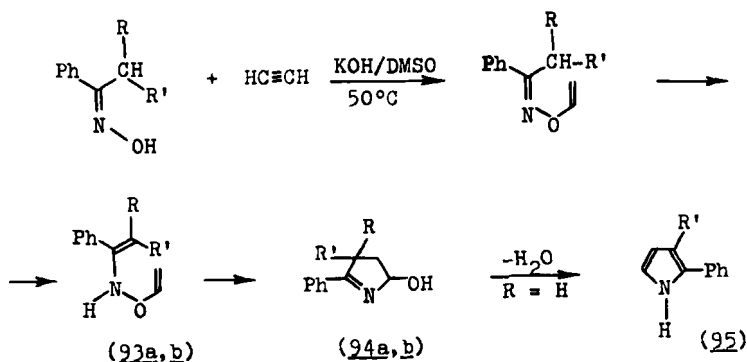
The need for the heterocyclization of *O*-vinylloximes to pyrroles to be carried out in a superbase medium arises from the fact that a [3,3]sigma-tropic rearrangement should be preceded by base-catalyzed prototropic isomerization of *O*-vinylxime to the *O,N*-divinylhydroxylamine (cf. Scheme 43, **87**, **90**) (84KGS1077).

## B. 4*H*-2-HYDROXY-2,3-DIHYDROPYRROLES

Despite the isolation of *O*-vinylloximes from the products of reaction of ketoximes with acetylene, and the demonstration of their conversion to pyrroles by superbase KOH/DMSO (see Section IV.A), the suggested (81MI4) intermediate stages of this rearrangement long remained unproved. The intermediate 4*H*-2-hydroxy-2,3-dihydropyrroles (**94**) (Scheme 45) were first isolated by Trofimov *et al.* (83KGS276).

As already shown (see Section IV.A), pyrolysis of *O*-vinylloximes in the absence of KOH/DMSO does not lead to 4*H*-2-hydroxy-2,3-dihydropyrroles. It has been assumed (84MI1) that the rearrangement is of specific anionic character and does not necessarily involve the formation of neutral *O,N*-divinylhydroxylamines (**87**, **90**, **93**). The intermediate anions (**96**) are likely to be more active in this case (Scheme 46).

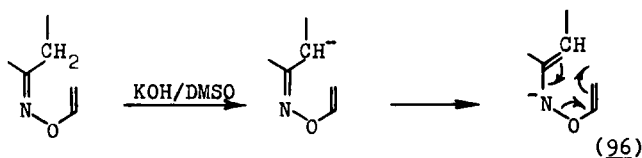
Two alkyl radicals at position 4 make impossible pyrrolization of the dihydropyrroles **94**, while with a hydrogen atom present in this position, the conversion to the corresponding pyrrole (**95**) happens with ease. A stable representative of these intermediates 4*H*-4,4-dimethyl-2-hydroxy-



R = R' = Me (**93a**, **94a**); R = H, R' = 1-Pr (**93b**, **94b**);

R' = i-Pr (**95**)

SCHEME 45



SCHEME 46

5-phenyl-2,3-dihydropyrrole (**94a**) was prepared from isopropyl phenyl ketoxime in 21% yield (m.p., 108–110°C) (83KGS276; 84MI1).

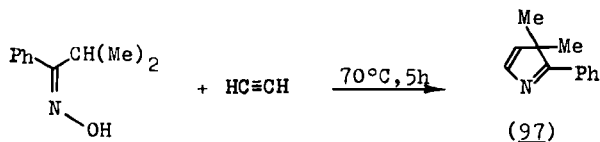
The  $^1\text{H-NMR}$  spectrum of the dihydropyrrole **94a** shows the following signals ( $\text{CDCl}_3$ , ppm): 7.57 (Ph), 6.90 (OH), 5.77 (t,  $\text{H}^2$ ), 2.24 (q,  $\text{H}^3$ ), 1.84 (q,  $\text{H}^{3'}$ ), 1.36 and 1.38 ( $\text{CH}_3$ );  $J_{23}$  6.0,  $J_{23'}$  6.5,  $J_{33'}$  12.75 Hz. Its IR spectrum (film,  $\text{cm}^{-1}$ ) also confirms the presence of necessary fragments, functions, and bonds: 1102, 3176, 3400 (OH), 1614 ( $\text{C}=\text{N}$ ), 1574 (Ph), 1328, 1445, 2870, 2964 (Me).

The UV spectrum of the dihydropyrrole **94a** contains two strong bands [ $\lambda_{\text{max}}$   $\log(\epsilon)$ ]: 202 (4.37), 241 (4.0). Similar spectral characteristics are displayed by 4*H*-4-isopropyl-2-hydroxy-5-phenyl-2,3-dihydropyrrole (**94b**) obtained from isobutyl phenyl ketoxime (m.p., 133–134°C, yield 26%). When stored or heated, the dihydropyrrole **94b** converts into 3-isopropyl-2-phenylpyrrole (**95**) with elimination of water.

### C. 3*H*-PYRROLES

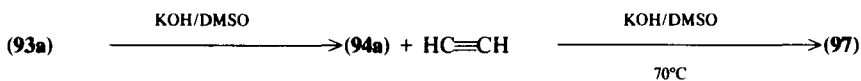
The reaction of isopropyl phenyl ketoxime with acetylene in the KOH/DMSO system was the first to show that ketoximes having only an "aliphatic" hydrogen atom in the  $\alpha$ -position with respect to the oxime function can serve as the starting material for the synthesis of inaccessible 3*H*-pyrroles.

Originally (85KGS1573) 3*H*-3,3-dimethyl-2-phenylpyrrole (**97**) was isolated from the reaction mixture by chromatography ( $\text{Al}_2\text{O}_3$ , hexane- $\text{Et}_2\text{O}$ , 2 : 1) in only 9% yield. In the author's laboratory, the yield of 3*H*-pyrroles has been raised to 40%.



The  $^1\text{H-NMR}$  spectrum of the pyrrole **97** has the following signals (acetone- $\text{D}_6$ , ppm): 1.39 (s,  $\text{CH}_3$ ), 6.30, 7.00 (dd,  $\text{H}^4$ ,  $\text{H}^5$ ,  $J_{45}$  3.2 Hz), 7.39–7.48, 8.04–8.09 (m, Ph); its IR spectrum (film,  $\text{cm}^{-1}$ ): 1370, 1387 (*gem*-dimethyl group), 1510, 1570 (Ph), 1675 ( $\text{C}=\text{N}$ ), 2880, 2930, 2970 ( $\text{CH}_3$ ), 3030, 3070, 3085 (Ph,  $\text{CH}=\text{CH}$ ), no absorption in the 3200–3600 region (OH).

The corresponding 2-hydroxy-2,3-dihydropyrrole (**94a**), the product of rearrangement of the *O*-vinylloxime **93a** (see Section IV.B), is converted to the 3*H*-pyrrole **97** under the conditions of the reaction with acetylene (85KGS1573), and this provides more evidence for the *O*-vinylloxime route to pyrroles from ketoximes and acetylene.



When there is a hydrogen atom in position 3, the 3*H*-pyrroles are not isolable as they readily convert into *NH*-pyrroles.

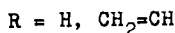
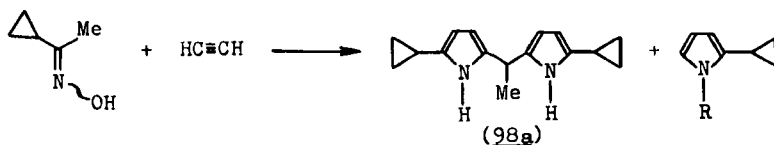
The formation of intermediate condensed 3*H*-pyrroles in the reaction of piperidine oxime with acetylene has been discussed (87KGS937, 87KGS1286, 87TH1) (see Section III.D).

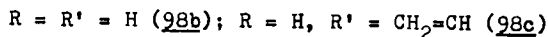
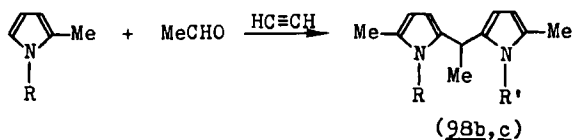
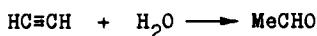
Thus, the reaction of ketoximes with acetylene catalyzed by the super-base pair KOH/DMSO offers the simplest approach to 3*H*-pyrroles, highly reactive, inaccessible, and so far poorly studied pyrrole isomers with no aromatic conjugation.

## D. DIPYRRYL ETHANES

Recently, (88ZOR1789) in the synthesis of pyrroles from ketoximes and acetylene (KOH/DMSO,  $95^\circ\text{C}$ , 5 hr, atmospheric pressure), the formation of dipyrrolethanes (**98a–c**) along with the normal products, *NH*-pyrroles and *N*-vinylpyrroles, was observed in a number of cases.

1,1-Di(2-cyclopropyl-5-pyrryl)ethane (**98a**) was isolated from the reaction mixture by chromatography ( $\text{Al}_2\text{O}_3$ , hexane- $\text{Et}_2\text{O}$ , 4:1) in 8% yield. The  $^1\text{H-NMR}$  spectrum of **98a** ( $\text{CDCl}_3$ , ppm): 7.73 (NH), 5.87 (t,  $\text{H}^4$ ,





SCHEME 47

$J_{34}$  2.5 Hz,  $J_{14}$  2.5 Hz), 5.71 (t,  $\text{H}^3$ ,  $J_{13}$  2.5 Hz), 4.04 (q,  $\text{CHCH}_3$ ), 1.52 (d,  $\text{CH}_3$ ), 1.68 (m, CH in cyclopropyl), 0.50–0.80 (m,  $\text{CH}_2$  in cyclopropyl). Its IR spectrum (film,  $\text{cm}^{-1}$ ) consists of 1500, 1580, 3080 (pyrrole ring), 3380 (N—H), 2865, 2920, 2965 (methyl and cyclopropyl C—H).

This side reaction seems to be common to all ketoximes, although the yield of other dipyrrol ethanes (98b,c) does not exceed 0.1% under normal conditions (88ZOR1789). It is likely that acetaldehyde formed due to the hydration of acetylene is involved in the condensation with pyrroles (Scheme 47).

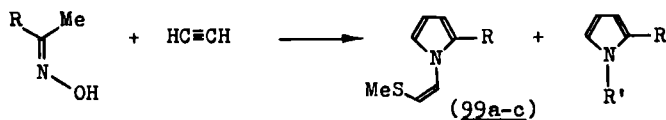
The reason for the particular ease of formation of 1,1-di-(2-cyclopropyl-5-pyrrol)ethane (98a) evidently consists in the high electron-donor ability of cyclopropyl, which increases the pyrrole ring nucleophilicity.

This condensation helps one understand why the yield of pyrroles from ketoximes and acetylene is reduced in some cases and consequently allows a more directed search for ways to overcome this obstacle. Optimization of this side reaction would make possible a one-pot preparation of valuable dipyrroles with cyclopropyl or vinyl substituents, such as 98a,c for example.

### E. 1-(2-METHYLTHIOVINYL)PYRROLES

A thorough investigation of the composition of reaction mixtures has revealed (86M12) that the KOH/DMSO-catalyzed synthesis of pyrroles from ketoximes and acetylene is accompanied by the formation of Z-1-(2-methylthiovinyl)pyrroles (99), which can be isolated in a yield of about 0.1% (Scheme 48). The pyrroles 99a-c are characterized in detail (86M13) by  $^1\text{H}$ -NMR (Table XXV).  $^{13}\text{C}$ -NMR, IR and mass spectra.

The  $^{13}\text{C}$ -NMR spectrum of pyrrole 99b ( $\text{CD}_2\text{Cl}_2$ , ppm) shows peaks: 109.64, 109.94 ( $\text{C}^3$ ,  $\text{C}^4$ ), 112.23 ( $\text{C}^5$ ), 123.23, 123.38 ( $\text{C}=\text{C}$ ), 129.21 (*C-meta*), 130.40 (*C-ortho*), 132.04 ( $\text{C}^2$ ), 133.39 (*C-ipso*), 133.68 (*C-para*). The IR spectrum of pyrrole 105b (film,  $\text{cm}^{-1}$ ) consists of: 710 (CH deforma-



(99)	R
a	Me
b	4-ClC <sub>6</sub> H <sub>4</sub>
c	4-(CH <sub>2</sub> =CHO)C <sub>6</sub> H <sub>4</sub>

SCHEME 48

TABLE XXV  
<sup>1</sup>H-NMR SPECTRA (CDCl<sub>3</sub>, PPM) OF 1-(2-METHYLTHIOVINYL)-PYRROLES (99a-c)

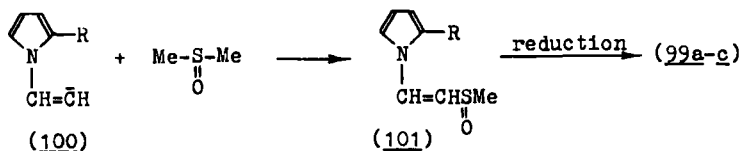
Pyrrole	R	H <sup>3</sup>	H <sup>4</sup>	H <sup>5</sup>	HCN	HCS
99a	Me	5.92 m	6.16 t	7.15 q	6.65 d	5.62 d
99b	4-ClC <sub>6</sub> H <sub>4</sub>	6.27 d		7.25 t	6.54 d	5.67 d
99c	4-(CH <sub>2</sub> =CHO)C <sub>6</sub> H <sub>4</sub>	6.26 m		7.00 m 7.29 m	6.58 d	5.66 d

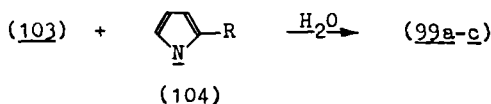
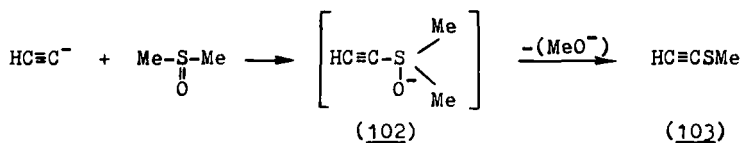
tions in pyrrole and benzene rings), 820, 890 (CH deformations in CH=CH), 1305 (pyrrole stretching), 1460, 1490, 1540, 1565 (pyrrole and benzene stretching), 2850, 2920, 2960, 2980 (CH<sub>3</sub> stretching), 3040, 3070, 3100, 3120 (CH stretching in CH=CH and benzene ring).

A probable pathway for the methylthiation observed is (86MI2) nucleophilic substitution at the sulfur atom in DMSO involving the carbanion **100** (precursor of 1-vinylpyrrole) followed by reduction of the intermediate vinylsulfoxide **101**.

Acetylenic carbanions or anion-radicals generated by a superbase system can serve as reducing agents (66JOC248; 81UK248).

Addition of the pyrrole anion **104** to the methylthioethyne **103**, which is assumed to be formed in small quantities from acetylene via the adduct **102**





SCHEME 49

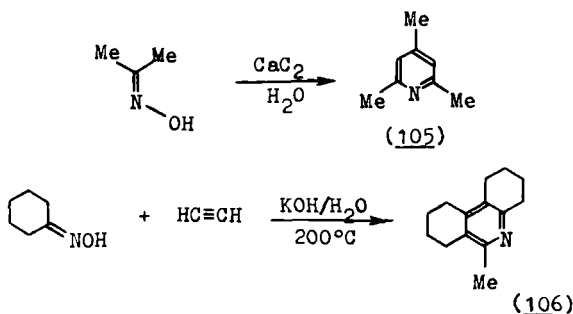
in the KOH/DMSO system (Scheme 49), is (86MI2) an alternative mechanism for the formation of **99**.

The Z-configuration of the vinyl moiety of pyrroles **99** corresponds to the latter scheme, since nucleophilic addition to the triple bond normally occurs as a concerted trans-process (78MI2).

## F. PYRIDINES

An attempt to reproduce the synthesis of *O*-vinylloximes (70ZOR2146) from oximes and acetylene in an aqueous solution by generating acetylene *in situ* from calcium carbide, gave pyridines instead of the expected products (75KGS1427). 2,4,6-Trimethylpyridine (**105**), for example, was obtained from acetoxime in 10% yield.

The reaction was carried out at 200–220°C in a rotating autoclave for 8 hr. Maximum pressure developed in the course of synthesis is 27 atm. Under these conditions, when acetylene instead of CaC<sub>2</sub> is used, the yield of pyridines grows to 20–30% (80KGS1299; 84MI1). Thus, from cyclohexanone oxime 6-methyl-1,2,3,4,6,8,9,10-octahydrophenanthridine (**106**) can be prepared.

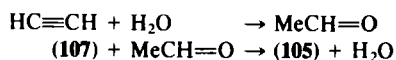


This promising reaction, however, was investigated (75KGS1427; 80KGS1299; 84MI1) only as a side process in the synthesis of pyrroles. These tentative experiments (75KGS1427) were not intended to increase yields of pyridines.

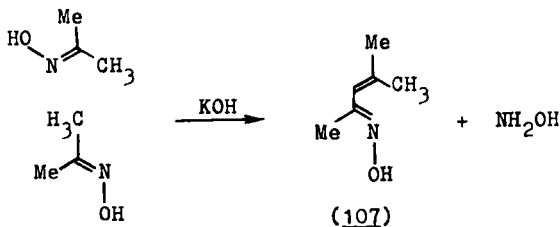
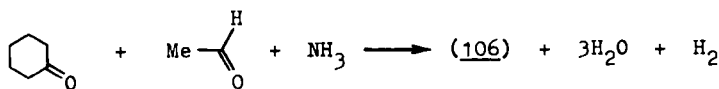
Since the formation of pyridines takes place in the presence of considerable amounts of water at temperatures greatly exceeding that optimal for the synthesis of pyrroles, the latter normally is not affected much by the reaction just mentioned.

As to its chemical nature, the condensation in question seems to be close to the known synthesis of pyridine derivatives by oxidative condensation of aldehydes and ketones with ammonia discovered by Chichibabin (55MI1).

In the case of ketoximes and acetylene in an aqueous alkaline medium the following condensation processes leading finally to pyridines are conceivable. (i) Dimerization of ketoximes with elimination of hydroxylamine (analog of crotonic condensation) (Scheme 50). (ii) Acetaldehyde condensation with the oxime of  $\alpha,\beta$ -unsaturated ketone **107**.



It is probable, however, that hydrolytic destruction of ketoximes to ketones and ammonia forms with acetaldehyde pyridines according to the Chichibabin scheme under the reaction conditions.



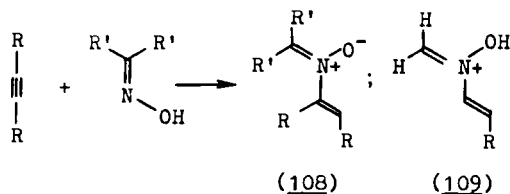
SCHEME 50

## G. ACETYLENIC ALCOHOLS

According to the literature data, the nature of the interaction of oximes with acetylenes depends on many factors. Winterfeldt and Kronh (69-CB2336) obtained oxazoles from ketoximes and dimethyl acetylenedicarboxylate by carrying out the reaction in DMSO at 20–25°C. Their work shows that the nitrogen atom of the oxime initially attacks the triple bond to form the intermediate **108** (Scheme 51).

A similar attack with formation of the intermediate **109** in the reaction of formoxime with methyl propyolate was observed by Japanese chemists (67T2641). This is in contradiction with a note (70TL25) concerning the preparation of *O*-adducts from dimethyl acetylenedicarboxylate and ketoximes. Transformations of this kind seem to be common to "activated" acetylenes since all attempts (76ZOR1180) to obtain in this way (under the same conditions) adducts of type **108** and **109** or *O*-vinylloximes from acetylene and its alkyl- and aryl-substituted derivatives were unsuccessful. The formation of intermediate *O*-adducts has been postulated by Heindel and Chun (71TL1439) in a report devoted to the synthesis of substituted imidazoles from alkylpropyolates and amidoximes. Failure, however, was encountered in an attempt to reproduce the synthesis of *O*-vinylacetoxime by direct vinylation of acetoxime with calcium carbide in an aqueous medium (70ZOR2146). Instead of *O*-vinylacetoxime, a symmetrical collidine was obtained (75KGS1427).

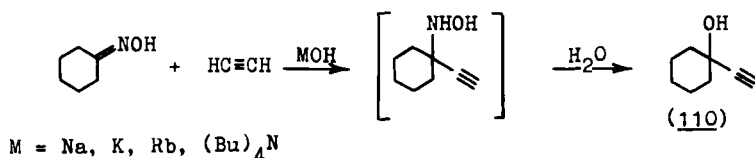
The interaction of  $\alpha$ -chloroximes with sodium arylacetylides (27MI1) or with ethoxyethynylmagnesium bromides (59G2466) starts with attack of the acetylene carbanion at the C—Cl bond to lead to isoxazoles. In systematic development of the reaction of acetylene with ketoximes, yielding substituted pyrroles (76ZOR1180; 80KGS1299; 81MI4), attention was given to occasional formation of significant amounts of  $\alpha$ -acetylenic alcohols, which indicates a possibility for oximes to be involved in the Favorsky-type alkynol synthesis. In a report by Trofimov *et al.*, (76ZOR-1180) the conditions for the formation of acetylenic alcohols from ketox-



R = CO<sub>2</sub>Me, R = alkyl

SCHEME 51





SCHEME 52

imes and acetylene are discussed with cyclohexanone oxime as an example (Scheme 52).

The reaction was carried out in dioxane, HMPA, and sulfolane as well as in mixtures of dioxane–DMSO (5 : 1 by volume) and water–DMSO (1 : 2) at 100–140°C with alkali metal (Li, Na, K, Rb, Cs) hydroxides, tetrabutylammonium hydroxide, and rubidium chloride examined as catalysts. All tests were run in an autoclave (1 L) at an initial acetylenic pressure of 12 atm. The most significant effect on the yield of 1-ethynylcyclohexanol (**110**) is that of the catalyst and the solvent. According to their diminishing efficiency, the catalysts examined are arranged as follows:  $\text{KOH} \geq \text{RbOH} > (\text{Bu}_4)\text{NOH} > \text{LiOH}$ ;  $\text{RbCl}$  failed to catalyze the reaction and in the presence of  $\text{CsOH}$ , resinification was observed. The alcohol **110** is formed most readily in aqueous DMSO, dioxane being next in efficiency (with account for the yield based on the oxime consumed). Addition of DMSO to dioxane does not improve the yield of **110**, and only trace amounts of this compound were obtained in HMPA and sulfolane.

The formation of ammonia always takes place. When heated with metal hydroxides some ketoximes partially regenerate ketones to liberate ammonia (54MI1). Nevertheless, cyclohexanone does not seem to be an intermediate product since, in a special run carried out with a mixture of cyclohexanone and ammonia (under otherwise equal conditions), a complicated mixture of products, containing no alcohol **110** was obtained. Cyclohexanone itself was nearly inert in runs with  $\text{LiOH}$ ,  $\text{NaOH}$  and tetrabutylammonium hydroxide, which provides evidence against its formation as an intermediate in the alkaline decomposition of the oxime.

Under optimal or close to optimal conditions for the synthesis of pyrroles from ketoximes and acetylene in the  $\text{KOH/DMSO}$  system, almost none of the acetylenic alcohols are formed.

## V. Influence of the Acetylene Structure and the Use of Acetylene Equivalents

### A. SUBSTITUTED ACETYLENES

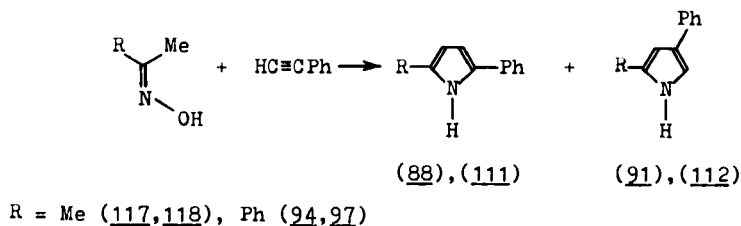
As shown with phenylacetylene (77KGS994), the formation of pyrroles may involve some monosubstituted acetylenes, incapable of prototropic

isomerization, and stable in the presence of strong bases. In this case, two phenylpyrrole isomers (**88** and **91**) can be formed depending on the direction of addition of the oximes to the triple bond (see Section IV.A, Scheme 43). When the reaction of acetone and acetophenone oximes was carried out with phenylacetylene (120–140°C, DMSO, 30–50% KOH of the ketoxime mass) only  $\alpha$ -phenylpyrroles **88** and **111** were obtained in 23 and 15% yield, respectively (Scheme 53) (77KGS994).

Later (84KGS1077), the two pyrrole isomers (**88** and **91**) were isolated in small yield (5–6%) in approximately equal quantities from the products of the reaction of acetophenone oxime with phenylacetylene carried out without solvent in the presence of the corresponding potassium oximate. The synthesis of 2,5-diphenylpyrrole (**88**) from acetophenone oxime and phenylacetylene was also performed (84KGS1077) in two stages (see Section IV.A, Scheme 48): initially the corresponding *O*- $\alpha$ -phenylvinylketoxime (**87**) was prepared (addition of acetophenone oxime to phenylacetylene in the presence of mercury acetate) and then it was heated at 45°C for 8 hr in the KOH/DMSO system (at this stage the yield of pyrrole **88** was 25%). Analogously, the isomeric 2,4-diphenylpyrrole (**91**) was obtained (17% yield) by heating (105°C, KOH/DMSO) the acetophenone oxime *O*- $\beta$ -phenylvinyl derivative **89** which had been prepared beforehand (70% yield) by adding the acetophenone oxime potassium salt to phenylacetylene (DMSO, 20–25°C).

Interestingly, if the addition of acetophenone oxime to phenylacetylene is carried out at a higher temperature (50°C) then, along with the *Z*-*O*- $\beta$ -phenylvinyl derivative **89** (Scheme 43), 2,5-diphenylpyrrole (**88**) is formed and not its isomer **91b**, which should result from rearrangement of the *O*-vinylloxime **89** detected in the reaction mixture (84KGS1077). This is likely to occur due to a considerably higher rate of rearrangement of the isomeric *O*- $\alpha$ -phenylvinylloxime **87**.

The harsher conditions for the conversion of the ether **89** to the pyrrole **91** are dictated by the need for the latter to initially transform from a *Z*- into an *E*-configuration, since only this one provides the necessary steric factors for the [3,3]-sigmatropic rearrangement. These rather scarce data indicate, however, that the range of application of the pyrrole synthesis



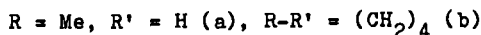
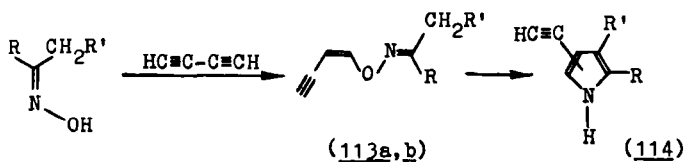
SCHEME 53

from ketoximes and acetylene is likely to be considerably wider than a short time ago.

Extension of the reaction to diacetylene might clear the way to the ethynylpyrroles **114**, promising monomers for conducting polymers and building blocks for the synthesis of new heterocycles. It turned out (76ZOR905) that, in an aqueous DMSO in the presence of catalytical amounts of KOH, diacetylene indeed added exothermically to ketoximes to form *O*-1-butene-3-vinylketoximes (**113**) (Scheme 54).

By varying the conditions of the reaction, either the *O*-vinylloximes **113** or black insoluble polymers, the products of deeper transformations of both diacetylene or the adducts, are obtained (80IZV2803). The pyrroles **114** could never be detected (GLC, TLC,  $^1\text{H-NMR}$  and IR spectroscopy). The best yield (36—41%) of the adducts **113** were achieved with the 10–30% water content, that of KOH being 1–2% of reaction mixture mass. Diacetylene was introduced into the solution with the nitrogen flow at a rate not permitting the reaction temperature to exceed  $60^\circ\text{C}$ . Lower concentrations of reactants in the solution also facilitate the formation of the adducts **113** by inhibiting polymerization. Thus, with the 20% acetoxime concentration, the yield of the *O*-(ethynylvinyl)oxime **113a** is 40% and drops to 30% when the 50% acetoxime concentration is the case. An increase in the alkali concentration also produces a negative effect on the reaction: with the 7% KOH content of the ketoxime mass, the yield of the adduct **113a** drops to 20%, and only traces of this adduct were obtained in a run with 30% KOH content. In spite of the fact that the reaction was performed with a large excess of ketoxime (especially at the initial stage), no addition of two ketoxime molecules to one diacetylene molecule was observed in either case.

According to  $^1\text{H-NMR}$  spectra, the adducts **113** are of the *Z*-configuration ( $^3J$  6.5–6.7 Hz). Consequently, the reaction of ketoximes with diacetylene is stereospecific and follows a trans-addition scheme. Since the process is facilitated by the addition of water, one may assume that nucleophilic addition to the  $\text{C}\equiv\text{C}$  bond also involves uptake of the proton delivered by the medium.



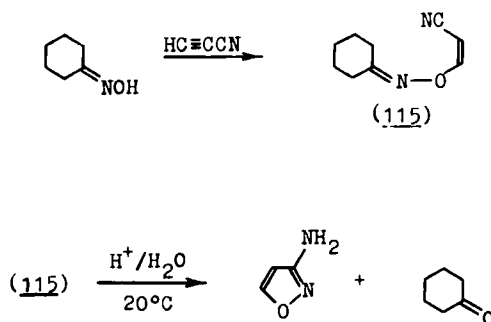
SCHEME 54

The *O*-(ethynylvinyl)ketoximes **113** are labile poorly stable liquids, which, however, can be distilled in vacuum, but quickly darken on storage especially in air. In the course of GLC analysis at 150°C, no decomposition of adduct **113a** was observed. At the same time, in the liquid phase, this compound does not withstand moderate heating (70–90°C), and even in solution it quickly and quantitatively turns to an insoluble black powder. Its IR spectrum is typical of polymers displaying a developed system of conjugated double bonds. In this spectrum, a very broad intense band in the 1500–1700  $\text{cm}^{-1}$  region with a maximum at 1650  $\text{cm}^{-1}$  dominates, whereas there are no frequencies of the terminal acetylenic group (2110, 3300  $\text{cm}^{-1}$ ) clearly expressed in the spectra of *O*-(ethynylvinyl)ketoximes. This indicates their polymerization involves the  $\text{C}\equiv\text{C}$  bond. Any deep reconstruction of the molecular backbone does not seem to occur in this case, since a narrow peak of the  $\text{C}=\text{O}$  stretching vibrations at 1120  $\text{cm}^{-1}$  characteristic of the adduct **113a** remains unchanged in the IR spectrum of the polymer. Except for the polymer, no other products of the thermolysis have been revealed.

Cyanoacetylene adds ketoximes in a solution of ethanol and *N*-methylmorpholine (5 : 2 by volume) at 0–20°C to form the corresponding *O*-vinyloximes(alkyldeniminooxyacrylonitriles) (70JAP33890). *Z*- $\beta$ -Cyclohexyldeniminooxyacrylonitrile **115**, for example, has been obtained in 96.5% yield.

There is no information concerning possible conversion of *O*-vinyloximes of the type **115** to pyrroles. However, it has been reported (70JAP) that under mild hydrolysis they can be converted to 3-aminoisoxazole (85% yield) with regeneration of ketone.

This provides evidence that these *O*-vinyloximes are highly prone to electrophilic addition of water across the  $\text{C}=\text{N}$  bond.



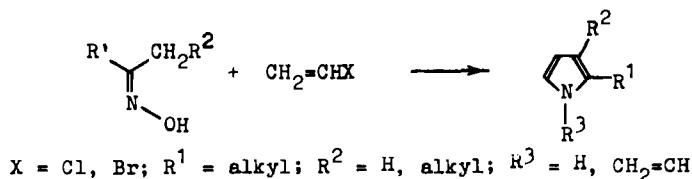
## B. VINYL HALIDES AND DIHALOALKANES AS ACETYLENE EQUIVALENTS

### 1. Vinyl Halides

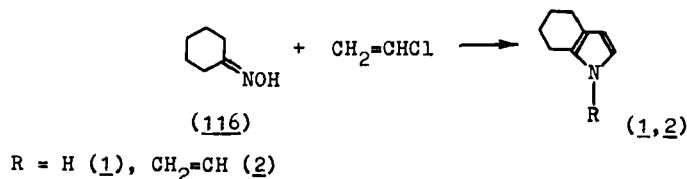
The reaction of ketoximes with vinyl halides at 80–130°C in the presence of alkali metal hydroxides and DMSO leads to pyrroles (80ZOR672) (Scheme 55). Varying the ratio of reactants and the conditions, it is possible to carry out the reaction selectively and obtain either pyrroles ( $R^3 = H$ ) in about 40% yield or their *N*-vinyl derivatives (yield to 35%).

4,5,6,7-Tetrahydroindoles (**1**, **2**) are prepared by the condensation of cyclohexanone oxime (**116**) with vinyl chloride in the presence of KOH in a DMSO medium at 90–140°C under atmospheric pressure (Scheme 56) (81MIP1; 86ZOR489).

To illustrate the main variations of the yield and ratio of the indoles **1** and **2**, depending upon the reaction conditions, GLC analysis of representative runs are given in Table XXVI. The best total yields of indoles **1** and **2** (50–60%) are obtained with the molar ratio of the oxime **116**/KOH/vinyl halides 1:6:5, 110–140°C, 3–6 hr (runs 3,4,7,8,10, Table XXVI). For a successful synthesis of indoles **1** and **2** it is necessary to gradually add alkali and ketoxime to DMSO heated to the reaction temperature under a fast inflow of vinyl halides. As the reaction temperature rises, the vinyl derivative **2** content grows and can exceed 10% at 140°C (run 8) for 3 hr. At 85–95°C, the yield of indoles **1** and **2** is considerably lower than that at higher temperatures (run 1) independent of the amounts of KOH and vinyl



SCHEME 55



SCHEME 56

TABLE XXVI

EFFECT OF REACTION CONDITIONS BETWEEN CYCLOHEXANONE OXIME (**116**) AND VINYL HALIDES ON THE YIELD OF 4,5,6,7-TETRAHYDROINDOLE (**1**) AND 1-VINYL-4,5,6,7-TETRAHYDROINDOLE (**2**) (SCHEME 56) (86ZOR489)

Run	116/KOH/vinyl halide molar ratio	time (hr)	Temp. (°C)	Conversion of <b>116</b> (%)	Yield (%)	
					Indole <b>1</b>	Indole <b>2</b>
1 <sup>a</sup>	1 : 21 : 15	3	95	82	26	10
2 <sup>a</sup>	1 : 6 : 5	1	110	99	40	3
3 <sup>b</sup>	1 : 6 : 5	3	110	76	46	8
4 <sup>b</sup>	1 : 6 : 5	6	110	98	32	22
5 <sup>c</sup>	1 : 6 : 5	3	110	81	22	traces
6 <sup>b</sup>	1 : 6 : 5	3	120	94	31	13
7 <sup>b</sup>	1 : 6 : 5	3	130	100	45	10
8 <sup>b</sup>	1 : 6 : 5	3	140	100	38	14
9 <sup>d</sup>	1 : 6 : 5	3	110	100	39	3
10 <sup>d</sup>	1 : 6 : 5	3	110	99	43	21

<sup>a</sup> Oxime was introduced at once into a suspension of alkali in DMSO.

<sup>b</sup> Alkali and oxime were added in batches every 30 min.

<sup>c</sup> HMPA instead of DMSO.

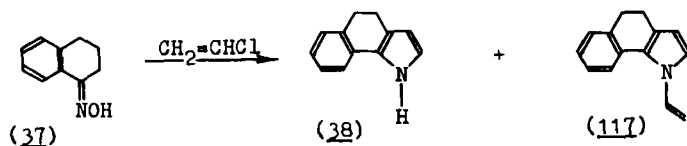
<sup>d</sup> With vinyl bromide.

chloride employed. When the reaction time is prolonged to 6 hr (run 4), the yield of the vinylindole **2** grows to 20% and higher. The replacement of DMSO by HMPA (as well as the replacement of KOH by NaOH) makes the process completely selective but diminishes, at the same time, the yield of **1** and **2** (run 5). The latter can be increased by using vinyl bromide instead of vinyl chloride (runs 9,10).

For a preparative synthesis of 4,5,6,7-tetrahydroindole (**1**), the following conditions have been recommended (86ZOR489): 110°C, 3 hr, the oxime **116**/KOH/vinyl chloride molar ratio 1 : 6 : 5, yield 46% based on the oxime consumed with oxime conversion of 75%.

4,5,6,7-Tetrahydroindole (**1**) was isolated by extraction of the reaction mixture with organic solvents (Et<sub>2</sub>O, benzene) and purified by distillation or recrystallization. This process for preparing 4,5,6,7-tetrahydroindole is simple enough, industrially feasible, safe, and based on the cheap and accessible raw materials. Cyclohexanone oxime is an inexpensive large-scale commercial product (caprolactam synthesis intermediate), vinyl chloride being one of the cheapest commercial vinyl compounds.

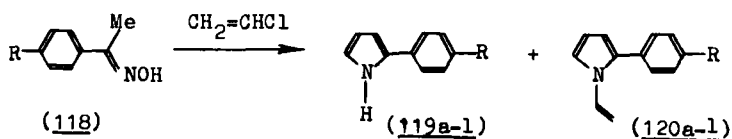
This novel synthetic route to pyrroles from ketoximes, based on the use of vinyl chloride instead of acetylene, allowed a one-pot preparation of almost inaccessible 4,5-dihydrobenzo[*g*]indole (**38**) and its previously un-



SCHEME 57

known *N*-vinyl derivative (117) from available  $\alpha$ -tetralone oxime (Scheme 57) (82ZOR2229).

The reaction was carried out in the KOH/DMSO system for 3–4 hr at 140–150°C. The *NH*- and *N*-vinyl derivatives 38 and 117 were separated by



(119)	R	Yield <sup>a</sup> , %	Reference
a	H	45 (7)	b
b	Me	39 (13)	b
c	Et	41 (11)	b
d	i-Pr	43 (11)	b
e	t-Bu	41 (14)	b
f	EtS	45 (7)	c
g	n-PrS	40 (8)	c
h	i-Pr	42 (6)	c
i	n-BuS	43 (6)	c
j	i-BuS	43 (12)	c
k	t-BuS	36 (8)	c
l	PhS	19	c

<sup>a</sup>The yield of the corresponding *N*-vinyl derivative (120) is given in brackets.

<sup>b</sup>(84KGS1359).

<sup>c</sup>(87KGS1486).

SCHEME 58

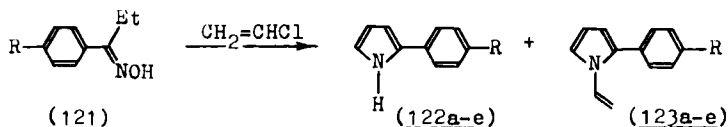
preparative TLC ( $\text{Al}_2\text{O}_3$ ,  $\text{Et}_2\text{O}$ –hexane 1 : 2), total yield 50%. 1-Vinyl-4,5-dihydrobenzo[*g*]indole (**117**) was isolated in 25% yield (after chromatographic purification). Its  $^1\text{H}$ -NMR spectrum has been described (82-ZOR2229).

$^{13}\text{C}$ -NMR spectra of indoles **38** and **117** show that introduction of the vinyl group in place of the hydrogen atom greatly deshields nearly all the carbon atoms of the condensed system.  $^{13}\text{C}$  Signals were assigned on the basis of analysis of spectra with complete or partial  $^{13}\text{C}$ — $^1\text{H}$  decoupling by comparison with the  $^{13}\text{C}$  chemical shifts of model compounds (81T3051).

Reaction of aryl methyl ketoximes (**118**) with vinylchloride in the KOH (5-fold molar excess)/DMSO system at  $120^\circ\text{C}$  and atmospheric pressure gave 2-arylpyrroles (**119**) and their *N*-vinyl derivatives (**120**) (Scheme 58) (84KGS1359, 84MI3; 87KGS1486).

The expected pyrroles could not be isolated from the reaction of aryl ethyl ketoximes with vinyl chloride at  $100^\circ\text{C}$  (4 hr, ketoxime/KOH molar ratio 1 : 2) in DMSO (84ZOR1960). These pyrroles were formed in low yields (2–7%) as established by use of  $^1\text{H}$ -NMR and IR spectroscopy.

However, recently it has been shown (88ZOR2436) that 2-aryl-3-methylpyrroles (**122**) can be synthesized from aryl ethyl ketoximes (**121**) using vinyl chloride instead of acetylene in good preparative yields (45–51%). The yield of the corresponding *N*-vinyl derivatives (**123**) is 4–6% in this case (Scheme 59).



(122)	R	Yield <sup>a</sup> , %
a	H	50 (6)
b	Me	45 (7)
c	Et	50 (5)
d	<i>i</i> -Pr	50 (6)
e	<i>t</i> -Bu	51 (5)

The yield of the corresponding *N*-vinylpyrrole (**123**) is given in brackets.

SCHEME 59



The best results were obtained at 130°C (3 hr) and with the oxime **121**/KOH ratio 1 : 6 in DMSO. The total yield of pyrroles **122** and **123** attains 56%. Replacement of methyl by ethyl in the alkyl moiety of ketoxime under comparable reaction conditions does not affect the total yield of pyrroles very much. However, on going from aryl methyl ketoximes (**118**) to aryl ethyl ketoximes (**121**), a downward trend in the yields for the corresponding *N*-vinylpyrroles (**123**) becomes evident. This is likely to be due to a decrease in polarizability and, consequently, to nucleophilicity of the 1-pyrrole anion as a result of distortion of the benzene and pyrrole ring coplanarity.

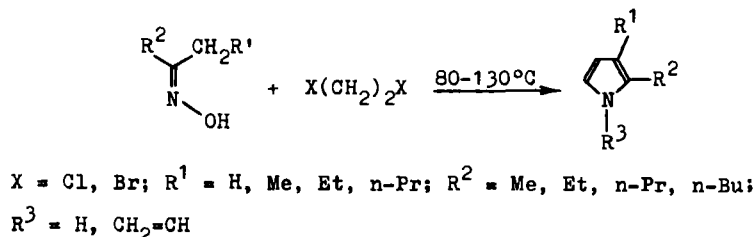
## 2. Dihaloalkanes

In the preparation of pyrroles and *N*-vinylpyrroles from ketoximes, along with vinyl halides, dihaloalkanes as acetylene equivalents can also be used. Pyrroles and *N*-vinylpyrroles are formed in a yield of about 30% in the reaction of ketoximes with dihaloalkanes in the presence of excess alkali metal hydroxide in DMSO (Scheme 60) (79IZV2840).

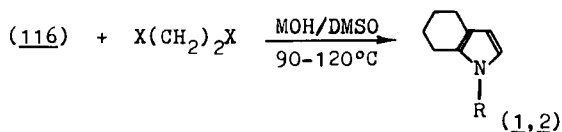
As with vinyl halides, depending on the reactant ratio and conditions, the reaction can be directed towards the predominant formation of non-vinylated pyrroles.

Some details concerning the synthesis of pyrroles from ketoximes and 1,2-dichloro- or 1,2-dibromoethanes in the KOH/DMSO system are described in a patent (82MIP1). The reaction proceeds smoothly and at a fairly high rate at 90–120°C. It is recommended that ketoxime, 1,2-dihaloethane, and KOH be taken in a molar ratio of 1 : (2–3) : (7–10) and the process carried out at 100°C for 2.5–6 hr. The preferable ketoxime/DMSO volume ratio is 1 : 10.

The reaction is performed as follows: KOH powder is dispersed in a ketoxime solution in DMSO. The dispersion thus obtained is quickly heated and a dihaloethane is added. The mixture is stirred for another half an hour at the same temperature, and then it is poured on ice and the



SCHEME 60



M = Li, Na, K; X = Cl, Br; R = H (1), CH<sub>2</sub>=CH (2)

SCHEME 61

product is extracted with diethyl ether or any other organic solvent immiscible with water. Pyrroles are normally purified by distillation. DMSO can readily be regenerated by distillation of the residual solution.

This process, likely based on vinyl chloride, is simple, efficient, safe, and convenient for engineering (it can easily be realized in the simplest conventional reactor at atmospheric pressure), and uses cheap and accessible raw material (dihaloethane and ketoximes). As stated previously, the interaction of ketoximes with dihaloethanes may also lead to *N*-vinylpyrroles. Occasionally the nucleophilic substitution of halogen by oximate anions, leading to ethyleneglycol diethers of ketoximes, becomes noticeable (see following).

A synthesis of 4,5,6,7-tetrahydroindole (1) and its *N*-vinyl derivatives (2) using 1,2-dihaloethanes (Scheme 61) has been described in detail (82KGS1202). In spite of lower yields of pyrroles, this version of the reaction may prove to be the most suitable for laboratories that have no acetylene or experience working with this gas.

The main trends in yield and ratio of *NH*- and *N*-vinyltetrahydroindoles (1, 2), depending on the reaction conditions, are illustrated by GLC analy-

TABLE XXVII  
EFFECT OF REACTION<sup>a</sup> CONDITIONS OF CYCLOHEXANONE OXIME (116) WITH DIHALOETHANES ON THE RATIO AND YIELD OF INDOLES 1 AND 2 (SCHEME 61) (82KGS1202)

Run	116/dihaloethane <sup>b/</sup> MOH <sup>c</sup> (mol)	Temp. (°C)	Reaction time (hr)	Yield of the product mixture <sup>d</sup> (%)	Composition (GLC) (%)		
					116	1	2
1	1:2:7	115	6	61	traces	83	17
2	1:2:7 <sup>e</sup>	93	6	33	4	94	2
3	1:3:12	115	4	53	traces	37	63
4	1:2:7 <sup>e</sup>	93	6	32	39	61	traces
5	1:2:7	115	4	52	54	46	traces
6	1:2:7	93	6	18	76	24	traces

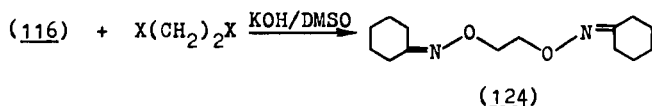
<sup>a</sup> In all runs DMSO is taken in a 10-fold excess of the oxime 116 mass.

<sup>b</sup> 1,2-Dichloroethane, except for run 4 (1,2-dibromoethane).

<sup>c</sup> KOH, except for runs 5 (NaOH) and 6 (LiOH).

<sup>d</sup> Based on the oxime taken.

<sup>e</sup> Water addition (10% of the reaction mixture mass).



SCHEME 62

sis of the mixtures isolated in some representative runs (Table XXVII). The best total yields (about 60% are achieved with the oxime **116**/dichloroethane/KOH/DMSO molar ratio 1 : (1–2) : 7 : 10, at 115°C, for 3–7 hr (Table XXVII, run 1). For the successful synthesis of tetrahydroindoles, alkali and dihaloethanes must be added batchwise to the ketoxime in DMSO. Otherwise, the formation of diether **124** via nucleophilic substitution of the halogen in 1,2-dihaloethane by the oximate anion competes with the main process (Scheme 62).

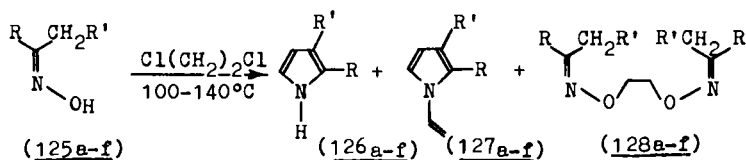
At the expense of lowering the yield to 30%, it is possible to attain 94–95% selectivity for the major products, 4,5,6,7-tetrahydroindole. As is the case in the reaction with free acetylene (75KGS1225), this is achieved by addition of small amounts of water (10–20%) to the reaction mixture (Table XXVII, run 2). It is convenient to dissolve the alkali in this water prior to feeding, which also facilitates batching of the two components. The conditions for runs 1 and 2 have been recommended (82KGS1202) for the synthesis of 4,5,6,7-tetrahydroindole. The latter is purified by recrystallization from hexane (the initial oxime can be removed from the reaction mixture by washing with a concentrated aqueous alkali solution). Thiylation of the mixture under the conditions described in (77KGS1636) is also of help when it is needed to get rid of the *N*-vinylindole **2** admixture. The addition of thiols to *N*-vinylpyrroles proceeds quantitatively to form high-boiling sulfides from which the tetrahydroindole **1** can be separated by distillation.

With an increase in the relative amounts of dihaloethane and alkali in the reaction mixture, the *N*-vinyl derivative **2** content of the mixture of products rises and can be brought to 60% and higher (run 3), the total yield exceeding 50%. This mixture can also be separated by crystallization of the tetrahydroindole **1** from hexane, liquid *N*-vinyltetrahydroindole **2** remaining in the mother liquor.

With 1,2-dibromoethane (run 4) under comparable conditions (run 2), somewhat poorer results are achieved: with the same total yield (about 30%), the crude product contains nearly 40% of the starting oxime. As in the reaction with free acetylene (see Section II.C.1), the substitution of KOH by NaOH and LiOH (run 5,6) makes the process completely selective, but leads to a sharp drop in the yield of products and in the oxime conversion.

In brief communications concerning the use of dialkyl ketoximes (79IZV2840; 81MI7, 81MI8) in this reaction, no comprehensive synthetic procedures are described. The experimental details for the synthesis of 2,3-dialkyl-substituted pyrroles from symmetrical and unsymmetrical dialkyl ketoximes and dichloroethane in the KOH/DMSO system (Scheme 63) were first discussed by Trofimov *et al.* (85KGS59).

Typical tendencies of the yields of the pyrroles **126** and **127** and side products 1,2-bis(alkylideniminoxy)ethanes **128** to depend upon the reaction conditions and the structure of dialkyl ketoximes are shown in Table XXVIII. The reaction is susceptible to a change in temperature, duration, KOH concentration and the method of introducing the latter into the reaction mixture as well as upon water added in the range 0.5–5%. The yield of pyrroles is also affected by the structure of ketoxime. The best total yields of pyrroles (30–60%) were obtained with the oxime **125**/dichloroethane/KOH molar ratio 1 : (2–3) : (7–10), 115–140°C, 1.5–6 hr (Table XXVIII, runs 1,3,5–7). As the temperature rises, the yield of pyrroles drops due to resinification. An increase in the reaction time affected the yield of pyrroles in an analogous manner. Elevation of the reaction temperature favors vinylation of the pyrrole formed at the first stage. The process selectivity can be controlled by introducing water into the reaction mixture. With the water content at 3–5% of the DMSO volume, the pyrrole vinylation stage is inhibited almost completely (Table XXVIII, run 1), making purification of the *NH*-pyrrole easier. Yet, the process of pyrrole vinylation takes place upon addition of 0.5–1% of water (runs 7,9).



(125-128)	R	R'
a	Me	H
b	Me	Me
c	Et	Me
d	Me	i-Pr
e	Me	n-Pr
f	Me	n-C <sub>5</sub> H <sub>11</sub>

SCHEME 63

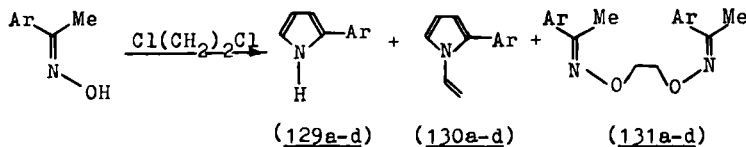
**TABLE XXVIII**  
**DEPENDENCE OF YIELD AND PRODUCT RATIO OF THE REACTION OF DIALKYL KETOXIMES WITH DICHLOROETHANE IN KOH/  
DMSO<sup>a</sup> ON THE REACTION CONDITIONS AND THE KETOXIME STRUCTURE<sup>b</sup>**

Run	Oxime <b>125</b>	Oxime/dichloro- ethane/KOH ratio <sup>c</sup> ,	Temp. (°C)	Reaction time (hr)	Yield (GLC) (%)		
					Pyrrole <b>126</b>	<i>N</i> -Vinyl- pyrrole <b>127</b>	Diether <b>128</b>
1	<b>125a</b>	1 : 2 : 7	112–115	3.5	30	1	2
2	<b>125a</b>	1 : 2 : 7	112–125	6.0	27	3	1
3	<b>125a</b>	1 : 2 : 3	110–126	2.0	31	traces	traces
4	<b>125a</b>	1 : 3 : 10 (5)	120–134	4.0	22	traces	6
5	<b>125b</b>	1 : 3 : 10	115–140	6.0	56	5	traces
6	<b>125c</b>	1 : 3 : 10	120–130	4.0	58	3	traces
7	<b>125d</b>	1 : 3 : 10 (1)	120–135	2.5	36	11	traces
8	<b>125e</b>	1 : 3 : 10	95–106	2.5	42	1	traces
9	<b>125f</b>	1 : 3 : 10 (1)	120–125	1.5	43	2	traces

<sup>a</sup> In all runs DMSO is taken in a 10-fold excess of the oxime mass.

<sup>b</sup> From reference (85KGS59), see also Scheme 63.

<sup>c</sup> In parentheses, water additive (% of the DMSO volume) is indicated.



(129-131)	Ar	Yield of 129, %
a	Ph	68
b	4-MeC <sub>6</sub> H <sub>4</sub>	64
c	4-MeOC <sub>6</sub> H <sub>4</sub>	69
d	4-ClC <sub>6</sub> H <sub>4</sub>	54

SCHEME 64

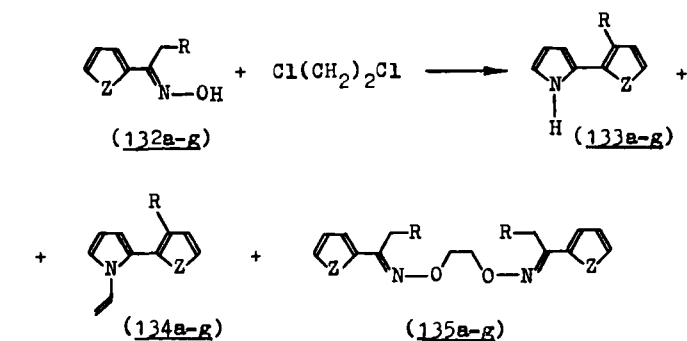
As in the reaction with free acetylene (see Section II.A), acetoxime is least prone to pyrrole formation (the total yield of the pyrroles **126a** and **127a** is about 30%). The *n*-alkyl methyl ketoximes **125b,e,f** react exclusively via the methylene group of the alkyl radical, whereas ketoxime **134** reacts by the methylene (preferably) and methyl groups to form pyrrole isomers.

The 1,2-bis(alkylideniminoxy)ethanes **128** formed in minor quantities (Table XXVIII) are side products. The **128** content of the reaction mixture increases in the case of a one-batch addition of alkali and dichloroethane to the ketoxime solution in DMSO. So, in order to suppress the substitution reaction, this operation should be performed batchwise.

In the reaction with 1,2-dichloroethane in KOH/DMSO (100–125°C), aryl methyl ketoximes form 2-arylpyrroles (**129**) in 70% yield (Scheme 64). The maximum yield of simultaneously formed *N*-vinylpyrroles (**130**) and diethers (**131**) does not exceed 12 and 21%, respectively (86ZOR492).

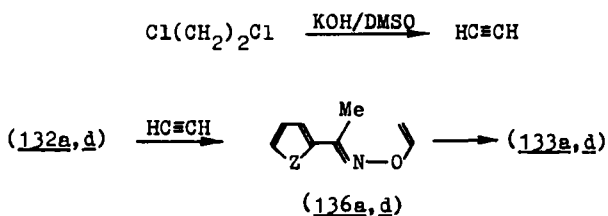
By the reaction of alkyl furyl(thienyl) ketoximes (**132**) with 1,2-dichloroethane in KOH/DMSO systems (M = Li, Na, K) at 100–135°C, a synthesis of 2-(2-furyl)- and 2-(2-thienyl)pyrroles (**133**) and their *N*-vinyl derivatives (**134**) in a yield of up to 54 and 20%, respectively, was performed (Scheme 65) [89KGS901].

Detection of the *O*-vinylloximes **136a,d** (Scheme 66) and the *O*-(2-chloroethyl)oxime **137** (Scheme 67) suggests two possible pathways for the formation of pyrroles from ketoximes and dichloroethane [89KGS901]. First, in a strongly basic medium, dichloroethane may act as an acetylene supplier (Scheme 66). Second, nucleophilic substitution of one chlorine atom in dichloroethane by the oximate-anion may lead to the *O*-(2-



(132-135)	Z	R	Yield of (133), %
a	O	H	47
b	O	Me	32
c	O	Et	25
d	S	H	54
e	S	Me	38
f	S	Et	34
g	S	n-Bu	42

SCHEME 65

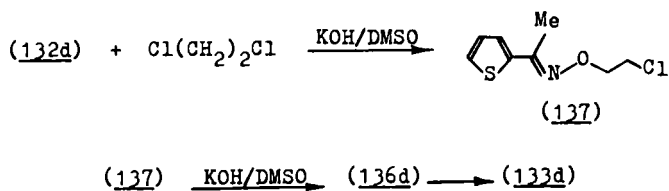


X = O (a), S (d)

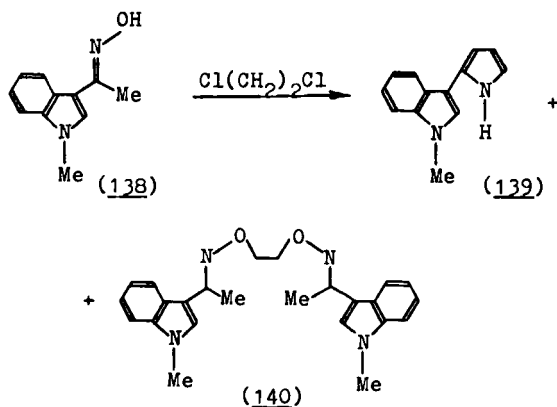
SCHEME 66

chloroethyl)oxime **137** (Scheme 67) with subsequent elimination of HCl to give the *O*-vinyloxime **136** and, further, the pyrrole **133**.

An attempt (83KGS356) to synthesize 3-(2-pyrrolyl)indole (**139**) from oxime 3-acetylindole (**138**) and dichloroethane with the oxime/dichloroethane/KOH/DMSO molar ratio 1:(1-2):7:10 and at 115°C has led mainly to diether (**140**) in 36% yield. Under these conditions the expected pyrrole (**139**) is formed in only negligible amounts (Scheme 68).



**SCHEME 67**



**SCHEME 68**

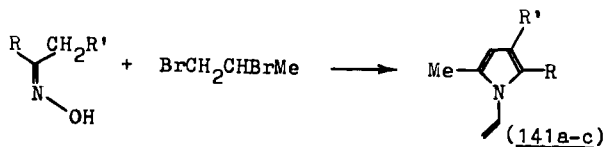
1,2-Bis(alkylideniminoxy)ethanes (**124,128,131,135,140**) are of potential value, particularly as chelating ligands for metal cations. A special investigation has been undertaken in order to increase their yields in the reaction of ketoximes with dichloroethane (88ZOR2538). As a result, special conditions have been found which allow 1,2-bis(organylideniminoxy)ethanes to be synthesized from oximes of dialkyl or alkyl aryl (hetaryl) ketoximes and 1,2-dichloroethane and an alkali metal hydroxide suspension in DMSO in yields up to 78%.

A synthetic route to substituted  $\alpha$ -methyl pyrroles (**141**) from ketoximes and 1,2-dibromopropane has been developed (Scheme 69) (88IZV2175).

The reaction was performed in DMSO for 3–4 hr at 140°C with the oxime/1,2-dibromopropane/KOH molar ratio 1:5:20 and ketoxime/DMSO ratio 1:30 (by mass).

The most probable sequence of reactions is this: superbase effected the transformation of 1,2-dibromopropane into the isomer pair methyl acetylene-allene (**142**), which further adds ketoxime to form the *O*-





(141)	R	R'	Yield, %
a	Ph	H	56
b	4FC <sub>6</sub> H <sub>4</sub>	H	21
c	(CH <sub>2</sub> ) <sub>4</sub>		42

SCHEME 69

vinyl oxime **143** then rearranges to the corresponding pyrrole (**141**) (Scheme 70).

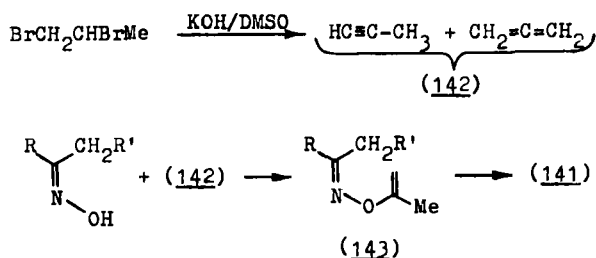
To obtain preparative yields of the pyrroles **141**, it is necessary that 1,2-dibromopropane must be added slowly (2–3 hr) to the oxime–KOH–DMSO suspension at the reaction temperature and rapidly stirred. The reported yields of the pyrroles **141** are not fully optimized.

The importance of the results obtained with dibromopropane lies in not only that a new simple procedure of introducing the methyl substituent into the position 2(5) of the pyrrole ring has been found, but also that an opportunity of utilizing alkynes and allenes in the reaction with ketoximes to prepare pyrroles is being outlined.

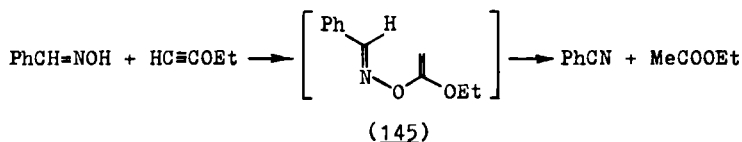
## VI. Mechanistic Aspects

### A. MODES OF THE OXIME–ACETYLENE INTERACTION

Depending on the reaction conditions and the structure of the reactants, the interaction of ketoximes with acetylenes may proceed in diverse directions, not all of them leading to pyrroles.

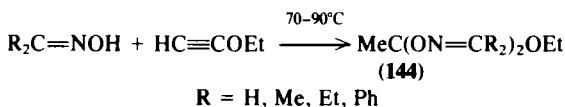


SCHEME 70



SCHEME 71

Oximes resemble alcohols in many respects and, consequently, they can add to the triple bond by the hydroxyl group. In fact, with ethoxyacetylene they form ortho-ester-like diadducts **144** (60RTC888).

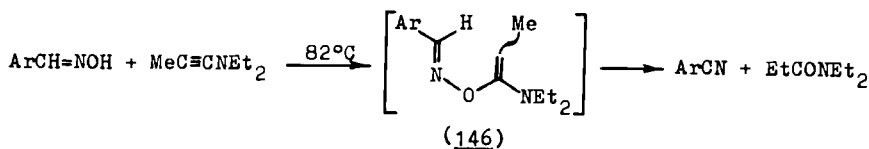


Under the same conditions, aldoximes (*E*- and *Z*-isomers), along with the formation of diadduct **144**, are sometimes dehydrated to nitriles, ethyl acetate being the second reaction product. This is explained (60RTC888) by decomposition of the intermediate *O*-vinylxime **145** (Scheme 71) which, however, has never been isolated.

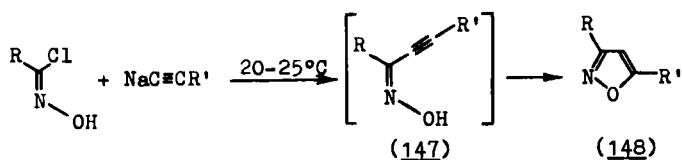
Nitriles were also obtained in the reaction of aldoximes with 1-(*N,N*-diethylamino)propyne via the supposed formation of *O*-vinylxime **146** (Scheme 72) (77S338). In both cases, the intermediate *O*-vinylximes (**145**, **146**), instead of pyrrolization, prefer decomposition into nitrile and carbonyl compounds.

The interaction of  $\alpha$ -chlorooximes with sodium acetylides, leading to the isoxazoles **148** (Scheme 73) (27M11; 59G2466), may also be regarded as an example of intramolecular addition of oxime hydroxyl to the triple bond in the intermediate **147**. However, in the formation of 3,5-di(ethoxycarbonyl)pyridine **149** from formaldoxime and ethylpropiolate (Scheme 74), the hydroxyl group remains inert with respect to the triple bond (67T2641).

In a similar manner (initially at the nitrogen atom, rather than at the hydroxyl group and then according to the scheme of 1,3-dipolar addition), acetoxime reacts with methyl esters of propiolic and acetylenedicarboxylic acids in DMF or DMSO to form, however, not pyridines but the 1,2-oxazole derivatives **150** (Scheme 75) (67AG722; 69CB2336, 69CB-2346).

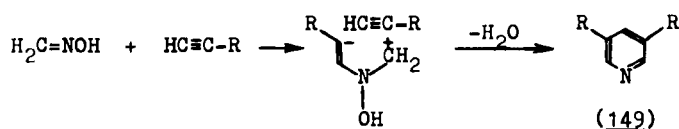


SCHEME 72



R = Ar, CCl<sub>3</sub>; R' = Ar (27MI1), EtO (59G2466)

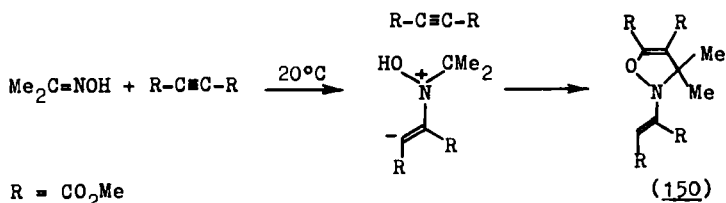
SCHEME 73



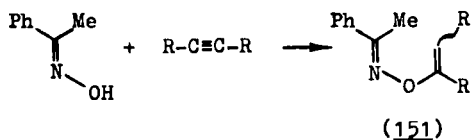
R = CO<sub>2</sub>Et

SCHEME 74

At the same time, according to the data of only one publication (70TL25), the interaction of ketoximes with acetylenedicarboxylates in the presence of sodium methylate in refluxing methanol leads to the *O*-adduct **151** (*Z:E*, 1:2), which forms the corresponding pyrrole upon thermolysis (Scheme 76).

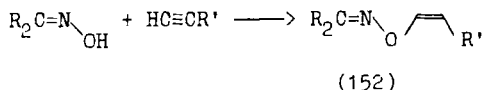


SCHEME 75

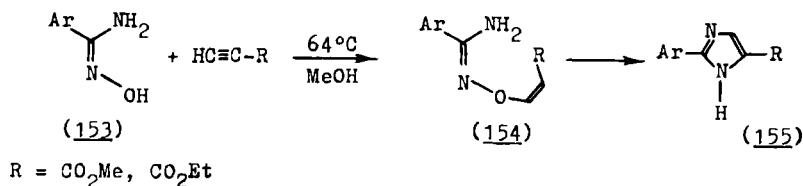


R = CO<sub>2</sub>Me

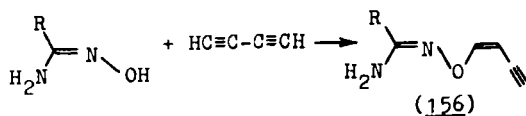
SCHEME 76



R = Me, Ph; R-R = (CH<sub>2</sub>)<sub>4</sub>; R' = CN (70JAP), C≡CH (76ZOR905, 80IZV2803)



SCHEME 77



R = Me, Ph

SCHEME 78

The reported synthesis of the simplest *O*-vinyloximes by the CaC<sub>2</sub>-assisted vinylation of oximes in an aqueous medium has been checked (75ZOR1141) and not reproduced. Instead of *O*-vinyloximes, pyridines are formed under these conditions (see Section IV.F).

With cyanoacetylene (70JAP33890) and diacetylene (76ZOR905, 80IZV2803), oximes give the *O*-vinyl derivatives **152** which, however, could not be rearranged to pyrroles (see Section V.B).

The rearrangement and cyclization to form imidazoles **155** take place during the interaction of amidoximes **153** with propiolic acid esters (Scheme 77) (71TL1439). The authors believe the intermediate *O*-adduct (**154**) to be subjected to rearrangement of the Claisen type involving three heteroatoms. Unfortunately, the intermediate **154** has not been completely identified. The latter has only been reported to possess a *Z*-structure (the coupling constant of olefinic protons is 6 Hz). The *O*-vinyloxime structure was assigned to this adduct on the basis that in acylation and alkylation reactions the oxygen atom of amidoximes is the most nucleophilic center (62CRV155), and that *O*-methyl ethers of amidoximes do not react with methyl propiolate.

In the reaction of amidoximes **153** with diacetylene in the presence of KOH in aqueous DMSO, the *O*-adducts **156** are formed (Scheme 78); no rearrangement thereof to ethynylimidazoles has been observed (76-IZV1430).

### B. PECULIARITIES OF OXIME BEHAVIOR IN HIGHLY BASIC MEDIA

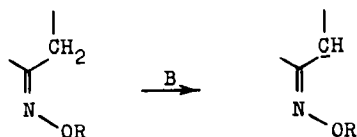
In the presence of superbases, ketoximes, their derivatives, and analogs are known to behave as CH acids, i.e., to be deprotonated at the CH<sub>3</sub> and CH<sub>2</sub> groups (75TL3889; 76JHC449, 76JHC607, 76TL1439). Regioselective deprotonation of ketoximes and methyl ethers thereof under the action of BuLi or lithium isopropylcyclohexylamide, i.e., elimination of the proton from the *cis*-position relative to the hydroxyl or methoxy group, has been reported (75TL3889; 76TL1439).

The authors (76TL1439) admit an attractive nonbonding interaction between the carbanionic  $\alpha$ -carbon atom and the oxygen in the forming system of six  $\pi$ -electrons. A stabilizing interaction of this kind has earlier been predicted by Epiotis (73JA3078) on the basis of quantum chemical calculations, and confirmed experimentally in the case of *Z*-1,2-difluoroethylene. A rough estimation of this stabilization for the carbanion of *O*-methyl dibenzyl ketoxime is 1.5 kcal/mol (75TL3889).

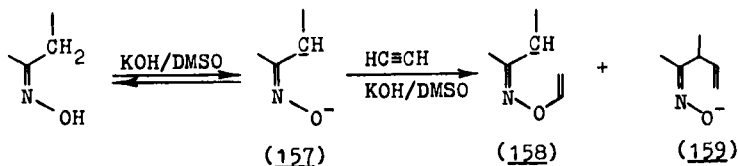
In building up the pyrrole ring from ketoximes and acetylene in the superbase KOH/DMSO medium, it is not only OH, but also the CH acidity of ketoximes leading to the anions **157–159**, that may play an important role (Scheme 79).

The existence of carbanions **157** and **158** in the presence of water is possible only in small quantities. However, in KOH/DMSO, part of the potassium hydroxide (employed in very large concentrations) is insoluble and present as a suspension. In this form, potassium hydroxide acts as a liquid phase drier which chemically binds water into hydrates. Moreover, it should be taken into consideration that DMSO itself also forms with water strong complexes (Me)<sub>2</sub>SO·2 H<sub>2</sub>O (64JPC3392; 78MI3), as well as hydrogen bonds stronger than those in water autoassociates (72JPC3050), and that altogether this significantly reduces the water activity. And, at last, the conditions for highly basic complex aggregates are created in this two-phase system (78MI2).

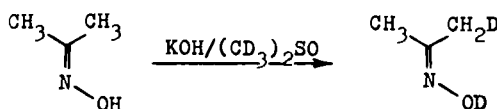
Evidence for the formation of carbanions from ketoximes and DMSO in the presence of large amounts of KOH is provided by partial deuterium exchange between DMSO-D<sub>6</sub> and the  $\alpha$ -position of ketoximes (75MI2; 76S281) in the synthesis of pyrroles, along with partial deuteration of hydroxyl.



R = H, Me; B - lithium isopropylcyclohexylamide (75TL3889)



SCHEME 79



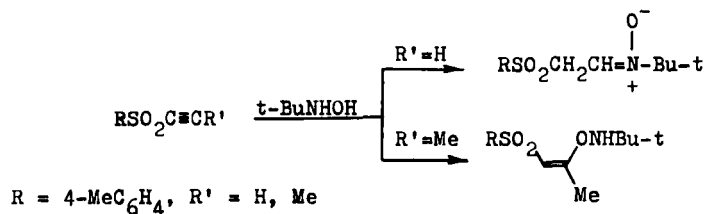
### C. IS THERE AN ALTERNATIVE TO THE O-VINYL OXIME PATHWAY?

The tridentate nature of the oximate-anion, i.e., its ability to act as *O*-, *N*-, and *C*-nucleophile, complicates analysis of the mechanism of the superbase-catalyzed heterocyclization of ketoximes with acetylene.

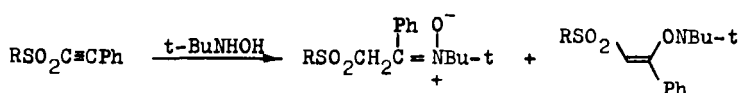
The capability of hydroxylamine derivatives to be either *O*- or *N*-nucleophiles in the reactions with acetylenic compounds depends on the structure of the latter. For example, *N*-*tert*-butylhydroxylamine can add to acetylenic sulfones either by the nitrogen atom or by the oxygen atom, depending on the character of the substituent at the triple bond (Scheme 80) (74JOC2641).

In the present case, the difference in the reaction direction could be explained in terms of steric hindrance for the triple bond to be attacked by the nitrogen atom when R = Me. In fact, however, the situation is more complicated, since in the same reaction when R = Ph, i.e., with a greater steric hindrance, a 3 : 2 mixture of *N*- and *O*-adducts is formed (Scheme 81) (74JOC2641).

Thus, the direction of addition of hydroxylamine derivatives to acetylenes is affected by not only steric, but also by electronic factors as well.



SCHEME 80



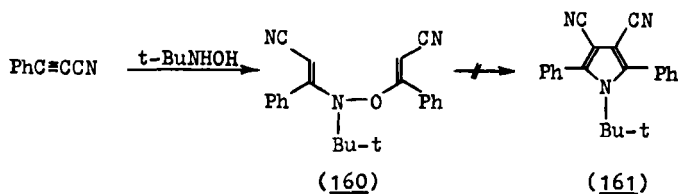
SCHEME 81

This conclusion has been confirmed by other authors (79CB2769) who examined the addition of monosubstituted hydroxylamines to various acetylenes. In most cases, they observed the formation of nitrones. With phenyl cyanoacetylene, however, the diadduct **160** was obtained due to participation of both the N—H and O—H bonds (Scheme 82).

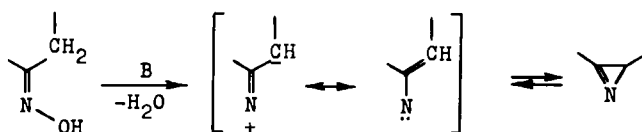
The diadduct **160** structurally corresponds to the intermediate in the synthesis of pyrroles via *O*-vinyloximes. However, no transformation of **170** to the corresponding pyrrole (**161**) has been observed.

In discussing the mechanism of synthesis of pyrrole from ketoximes and acetylene, one cannot leave out the possibility that an azirine intermediate, or its open form, a 1,3-dipole (75MI1, 75MI2, 75MI3, 75KGS360; 79MI1, 79MI2, 79MI3; 80KGS1299) or vinylnitrene (79MI1, 79MI2, 79MI3), may be involved in the reaction, since the capability of ketoximes to undergo the strong base-induced 1,3-dehydration (Scheme 83), thus cyclizing to azirines, is well known (the Hoch–Campbell reaction) (34MI1; 39JOC198; 43JOC99, 43JOC103; 44JOC184; 53JA2959; 57JOC1036, 63BCJ1434; 65MI1; 66MI3; 75BSF173; 76CPB1083).

In the light of all the data collected, the following heterocyclization mechanisms may be considered (Scheme 84): (i) [3,3]-sigmatropic shift in an intermediate *O*-vinyloxime; (ii) nucleophilic attack on acetylene by

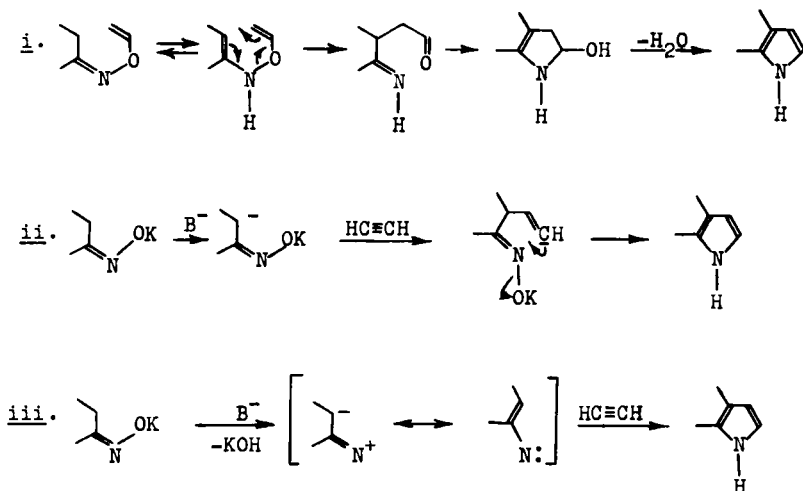


SCHEME 82



B = RMgX, LiAlH<sub>4</sub> and the like

SCHEME 83



SCHEME 84

the carbanion of ketoxime (only key stages are shown in the scheme); (iii) 1,3-dehydration of ketoxime and addition of the resulted 1,3-dipole (or the corresponding vinylnitrene) across the triple bond.

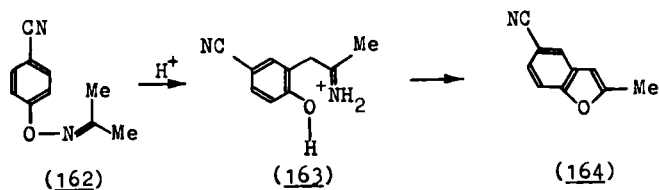
The first mechanism is favored at present (see Sections IV.A–C): in many cases the formation of pyrroles clearly involves *O*-vinyl derivatives.

It is not clear, for example, why the expected ethynylpyrroles cannot be obtained by use of diacetylene, although the corresponding *Z*-*O*-( $\beta$ -ethynylvinyl)oximes are formed fairly readily (see Section V.B).

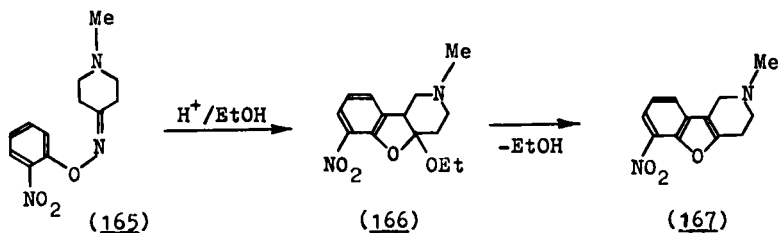
Interestingly, *O*-aryloximes **162**, close analogs of *O*-vinylloximes, rearrange to furans rather than to the corresponding pyrroles (**164**) (66TL5225; 67JHC413, 67TL407, 67TL859, 67TL2867; 74MI6) (Scheme 85).

A rearrangement intermediate, protonated 4-hydroxy-3-(2-iminopropyl)benzonitrile (**163**) proved to be isolable (67TL2867). Analogously, from 1-alkyl-4-nitrophenyloximinopiperidine (**165**) in ethanolic HCl, 2-methyl-6-nitro-1,2,3,4-tetrahydrobenzofuro[3,2-*c*]pyridine (**167**) was ob-





SCHEME 85

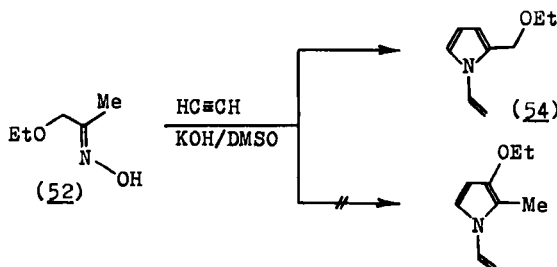


SCHEME 86

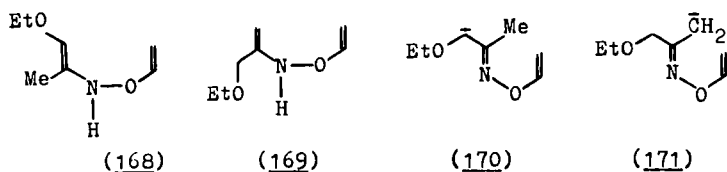
tained. The intermediate acetal, 4*a*-ethoxy-2-methyl-5-nitro-1,2,3,4-4*a*,-9*b*-hexahydrobenzofuro[3,2-*c*]pyridine (166) appeared to be isolable (Scheme 86) [71JCS(C)53, 71JOC1061].

The results (78IZV2426; 80ZOR410) concerning the interaction of  $\alpha$ - and  $\beta$ -hydroxyalkyl ketone oximes with acetylene, discussed in Section III.E, may be regarded as evidence for the important role of carbanions at the first stages of the ring formation. It is in these terms that the observed regiospecificity of the reaction of 1-ethoxy-2-propanone oxime (52) with acetylene (Scheme 87) can be rationalized (78IZV2426).

Of two possible key intermediates in the rearrangement of *O*-vinylloximes (168 and 169), intermediate 168, in which the internal double bond is adjacent to the nitrogen atom, is additionally stabilized by *p*- $\pi$ -conjugation with the oxygen atom, and may be the more stable (Scheme 88).



SCHEME 87



SCHEME 88

This intermediate, however, must lead to 1-vinyl-2-methyl-3-ethoxypyrrole, which is not the case. Otherwise, of two possible carbanions (**170** and **171**), the latter seems to be more stable since it is free from destabilizing interaction of the negative charge with the lone electron pairs of the neighboring oxygen atom, which does occur in the carbanion **170**. This is likely to be responsible for the regiospecific formation of 1-vinyl-2-ethoxymethylpyrrole (**54**).

In conclusion, the experimental material is in accordance with the *O*-vinylation mechanism. It is probable, however, that depending upon the reaction conditions and the structure of reactants, some alternative routes shown in Scheme 84 are realized in particular cases. At the same time, it should not be ignored that any scheme, even those that seem to be most reasonable, cannot be considered as adequate unless they explain why the pyrrolization of ketoximes with acetylene succeeds only in the presence of specific superbase systems (strong base/DMSO).

## VII. Conclusion and Outlook

Systematic research on this novel synthesis of pyrroles and especially of *N*-vinylpyrroles from ketoximes and acetylene is in progress. This is expected to lead to not only further extension of the preparative possibilities of the reaction, but also to discovery of new versions and analogs. The increased access to *N*-vinylpyrroles stimulates more and more synthetic and theoretical investigations in this field as well as work dealing with polymerization and practical application of these compounds (84MI1). For the 20 years since its discovery, the reaction of ketoximes with acetylene has become popular as a reliable preparative tool for wide application in the chemistry of pyrroles.

Thus, the present review is not only a summary, but also an introduction into a novel developing area where there is much to be done.

## ACKNOWLEDGMENTS

This review would not have been possible without the skillful and untiring activity of my co-workers and collaborators: A. I. Mikhaleva, S. E. Korostova, L. N. Sobenina, E. A. Petrova, R. N. Nesterenko, S. G. Shevchenko, A. M. Vasil'tsov, O. V. Petrova, M. V. Markova, E. A. Polubentsev, and V. N. Salaurov.

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